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Organocatalytic C–H Bond Arylation of Aldehydes to Bis-heteroaryl Ketones

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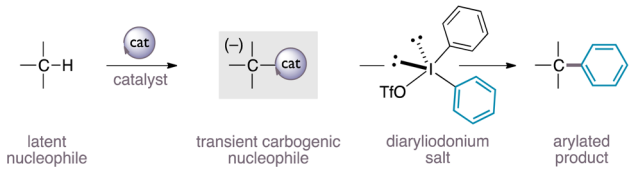
Supporting Information

ABSTRACT: An organocatalytic aldehyde C–H bond arylation process for the synthesis of complex heteroaryl ketones has been developed. By exploiting the inherent electrophilicity of diaryliodonium salts, we have found that a commercial N-heterocyclic carbene catalyst promotes the union of heteroaryl aldehydes and these heteroaromatic electrophile equivalents in good yields. This straightforward catalytic protocol offers access to ketones bearing a diverse array of arene and heteroarene substituents that can subsequently be converted into molecules displaying structural motifs commonly found in medicinal agents.

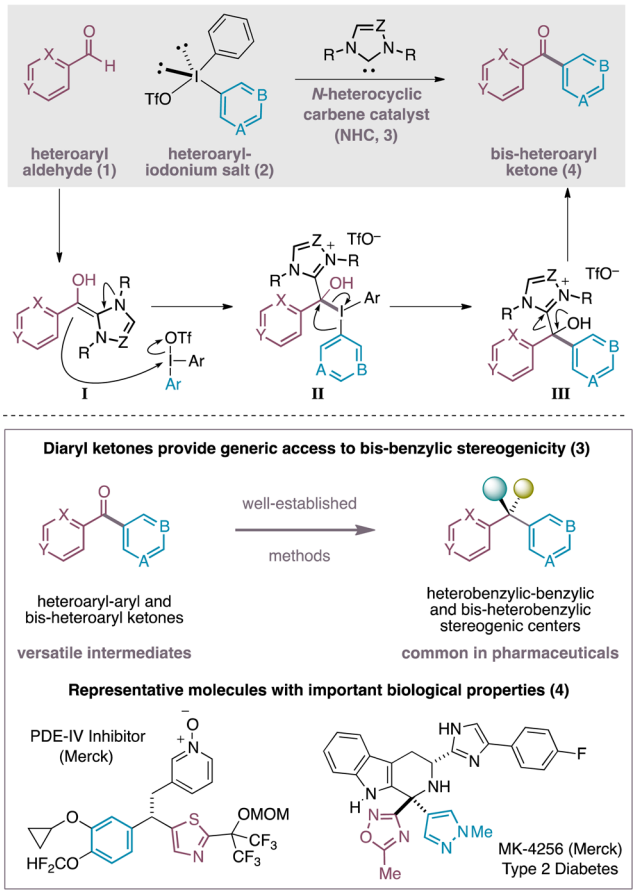
Diaryliodonium salts have become an increasingly exploited class of aryl transfer reagents that frequently behave as aromatic electrophiles.[1] This reactivity profile stems from the electrophilic nature of the iodine(III) center, making it susceptible to attack from nucleophiles.[2] Aryl transfer to nucleophiles such as alkoxides and enolates is proposed to occur through initial attack at iodine followed by ligand coupling and has resulted in a number of useful carbon–aryl and heteroatom–aryl bond-forming processes.[1,3] Despite this utility, the development of catalytic processes using diaryliodonium salts has been dominated by the use of transition metals, which typically operate via oxidative insertion. The metal–aryl intermediates are able to function in traditional Pd-catalyzed cross-couplings or serve as reactive aromatic electrophiles in Cu-catalyzed reactions with a range of π-nucleophiles.[1,4−6] Given the intrinsic electrophilicity of diaryliodonium salts, we were surprised that a contrasting strategy based on catalytic generation of carbogenic nucleophiles that react with these aryl transfer reagents directly to form carbon–aryl bonds (eq 1) has yet to be fully exploited.[7]

Electrophilic arylation via catalytic nucleophile activation strategy (1)



Herein we report the successful development of this concept through an organocatalytic aldehyde C–H arylation process (eq 2). In this transformation, an N-heterocyclic carbene (NHC) catalyst reacts with an aldehyde to form a transient carbogenic nucleophile, which reacts with the diaryliodonium salt. This combination leads to a potentially useful and as yet unexplored means of aryl transfer to form carbon–aryl bonds to traditionally non-nucleophilic molecules. Moreover, this straightforward aldehyde C–H bond arylation process forms a range of complex heteroaryl aryl ketone and bis-heteroaryl ketone products from readily available starting materials and should find broad utility in synthetic applications.

C–H arylation strategy using NHC catalysis and diaryliodonium salts (2)



Diaryl ketones are multifaceted compounds that function as components of pharmacophores, photolabels and photosensitizers, organic electronics, and polymers.[8a−e] Furthermore, manipulation of the carbonyl group provides a generic entry into molecules containing bisbenzylic functionality (eq 3). Of particular importance to medicinal chemists are compounds

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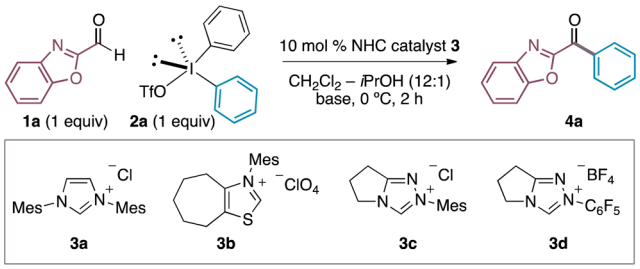
displaying heterobenzylic–benzylic and bis-heterobenzylic motifs (eq 4).[9] Classical methods for the formation of diaryl ketones include the addition of arylmetal species to carbonyl compounds[10,11] and Friedel–Crafts acylation reactions. However, the presence of aromatic heterocyles can limit these strategies, as organometallic reagents can be incompatible with heteroaromatic nuclei[12] and Friedel–Crafts acylations usually work best with π-rich arenes and sometimes result in isomeric mixtures. An alternative C_{acyl}–C_{aryl} bond formation strategy has been realized through Pd-catalyzed cross-coupling reactions of activated carboxylic acid derivatives[13] and carbonylative processes.[14] More recently, metal-catalyzed C–H arylation of aldehydes has provided new pathways for the construction of these molecules.[15,16] Related to this strategy, diaryl ketone formation from aldehydes has been realized using NHC catalysis[17] through reactions with aromatic electrophiles such as activated aryl halides via S_NAr-type reactions[18] or with benzynes.[19] Despite the sophistication of these catalytic methods, the majority of examples form benzophenone derivatives, and the number of heteroaromatic coupling partners is limited. Driven by the need for a catalytic method for regioselective diaryl ketone formation that can incorporate a broad range of heteroaromatic nuclei, we envisioned that these challenges could potentially be met through the use of diaryliodonium salts. These aromatic electrophiles react with precise regiocontrol upon combination with nucleophiles, are readily prepared and stable reagents, and can transfer aryl or heteroaryl groups. Taken together with the reactivity of acyl anion equivalents, which are readily accessible through the powerful NHC catalyst activation mode, we speculated that the reaction of heterocyclic aldehyde **1** with NHC **3** would form the putative Breslow intermediate **I**,[20] a nucleophilic species that could attack the iodine(III) center of diaryliodonium salt **2** (eq 2). In the resultant iodane species **II**, aryl transfer would constitute the key C–C bond-forming event, affording tertiary carbinol **III**. Release of the NHC catalyst would form the desired bis-heteroaryl ketone **4** and complete the catalytic cycle.

We began our investigation by using benzoxazole-2-carboxaldehyde (**1a**) as a representative heterocyclic substrate in combination with diphenyliodonium triflate (**2a**) and a selection of commonly encountered NHC catalyst precursors **3** (Table 1, entries 1–4). After assessing four commercially available catalysts, we were delighted to find that triazolium salt **3d**, developed by Rovis,[21] was the most effective in promoting the desired bond-forming process to give ketone **4a**. This is consistent with recent reports by Rovis and co-workers demonstrating the suitability of N-C_6F_5-substituted triazolium catalysts in facilitating Stetter reactions of heterocyclic aldehydes.[22] Key results of our optimization included an improvement in yield when 4-dimethylaminopyridine (DMAP) was used as the base to generate the carbene (entries 5–10) and the observation that including a protic additive was beneficial for homogeneity of the reaction mixture. It is important to emphasize that the reaction employs an equimolar ratio of diphenyliodonium triflate and aldehyde and uses a commercially available NHC catalyst.

After establishing the optimal reaction conditions, we applied this new arylation protocol to a series of heterocyclic aldehydes, producing heteroaryl-phenyl ketones in good yields (Table 2, **4b–l**). Aliphatic aldehydes could also be arylated in this process (**4m**). Beyond phenyl group transfer, symmetrical diaryliodonium salts displaying a range of substituents could be incorporated without loss of efficiency (**4n–r**). Particularly noteworthy are diaryl ketones that could be selectively formed

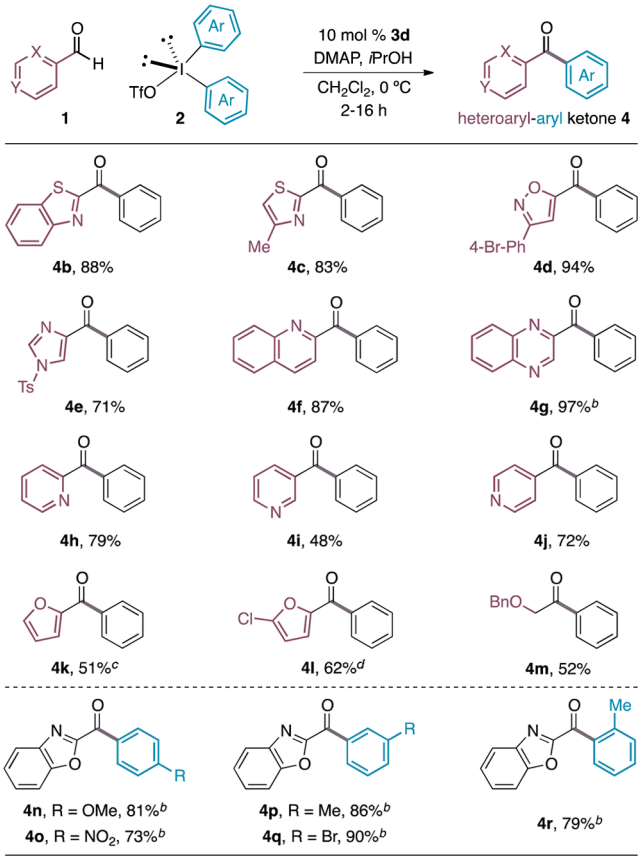
Table 1. Evaluation of NHC Catalysts and Bases



entry	catalyst	base (equiv)	yield of **4** (%)[a]
1	**3a**	iPr_2NEt (1.0)	0
2	**3b**	iPr_2NEt (1.0)	17
3	**3c**	iPr_2NEt (1.0)	19
4	**3d**	iPr_2NEt (1.0)	77
5	**3d**	KHMDS (1.0)	70
6	**3d**	K_2CO_3 (1.0)	43
7	**3d**	DBU (1.0)	70
8	**3d**	DMAP (1.0)	79
9	**3d**	**DMAP (1.5)**	**98 (91[b])**
10	**3d**	iPr_2NEt (1.5)	83
11	**3d**	DMAP (no *i*PrOH) (1.5)	86

[a]Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated yield.

Table 2. Scope of Heteroaryl Aldehydes: Phenylation[a]



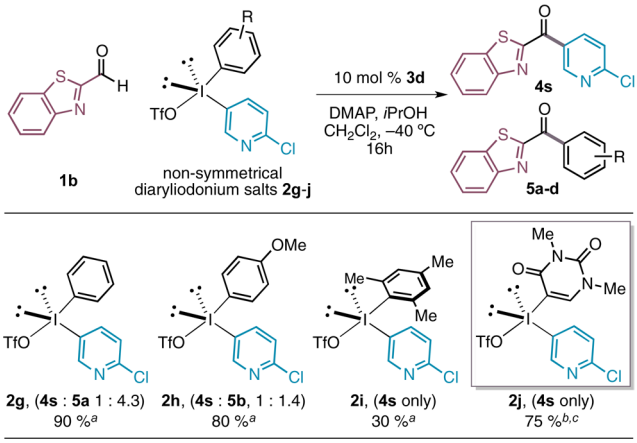
[a]Isolated yields are shown. [b]At −40 °C. [c]20 mol % **3d**. [d]15 mol % **3d**.

with substitution patterns that are "nonstandard" on the basis of the principles of Friedel–Crafts acylation reactions (**4o–r**).

Our next challenge was to apply this method to synthesize bis-heteroaryl ketones. Compared with their symmetrical

counterparts, nonsymmetrical heteroaryliodonium salts would be advantageous for this purpose because of their relative ease of synthesis and the more economical use of the transferring group. Observations from the literature suggested that the more electron-deficient aryl moiety should be transferred from the iodine(III) center after nucleophilic attack.[3b,23] However, when we tested salts **2g** and **2h**, displaying simple phenyl and anisyl groups, respectively, alongside the pyridyl unit, the selectivity of the aryl transfer was poor (Scheme 1). Although the sterically

Scheme 1. Selectivity of Aryl Transfer[a]

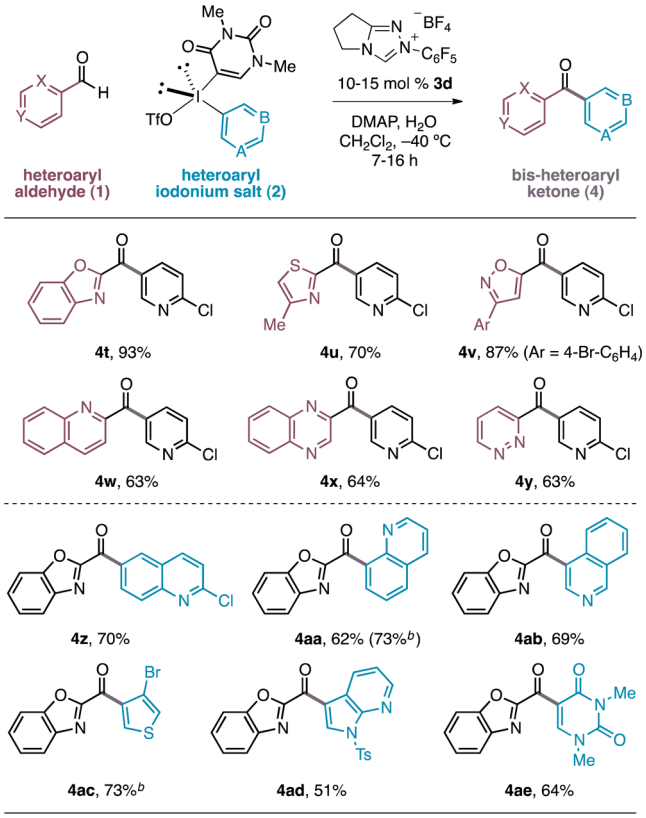


[a]Yield determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated yield. [c]H_2O was used instead of *i*PrOH.

hindered mesityl salt **2i** resulted in selective formation of bis-heteroaryl ketone **4s**, the yield was low. This was surprising, as sterically demanding aryl groups tend to undergo preferential aryl transfer.[24] In searching for an alternative, we wondered whether nonsymmetrical uracil–aryl iodonium salts[25] could be adapted to our purposes. Uracil–pyridine salt **2j** was readily prepared,[26] and when it was subjected to the reaction conditions, ketone **4s** was formed exclusively in 75% yield. While a precise rationale for the aryl transfer selectivity is unclear, these results suggest that the usual rules governing selectivity do not operate during this process.

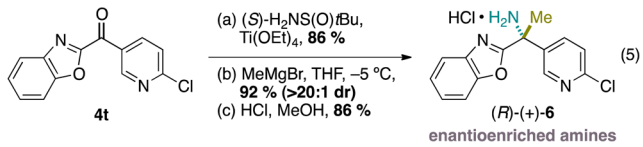
Using uracil–heteroaryl iodonium salts, we were able to demonstrate further the value of this process by constructing a range of bis-heteroaryl ketones (Table 3). Five-membered heteroaryl aldehydes performed well, resulting in high yields of bis-heteroaryl ketone products (**4t–v**). Six-membered heteroaryl aldehydes showed slightly lower reactivity but nevertheless combined productively with **2j** to form the desired products in synthetically useful yields (**4w–y**). The transfer of the pyridyl group was observed as the only detectable outcome in all cases. We also found that a variety of uracil–heteroaryl iodonium salts were compatible with the new coupling process to heteroaryl aldehydes; electron-deficient heteroarenes (**4z–ab**) and an electron-rich thiophene derivative (**4ac**) were accommodated well by this protocol. Important pharmacophores such as azaindoles could also be incorporated into bis-heteroaryl ketones (**4ad**). Finally, in a surprising outcome, the uracil motif was selectively transferred when uracil–3-(*N*-methylpyrazole) iodonium triflate was tested as a coupling partner, further reflecting the subtle balance of factors influencing aryl transfer (vide supra).

Table 3. Formation of Bis-heteroaryl Ketones: Scope[a]



[a]Yield of isolated products. [b]Using symmetrical iodonium salt.

To illustrate the potential utility of our new process, we demonstrated how bis-heteroaryl ketones can be converted into enantioenriched molecules (eq 5). Ellman imine formation



(5)

from **4t** (not shown),[27] addition of MeMgBr in high yield and diastereoselectivity (92% yield, >20:1 dr), and auxiliary cleavage furnished optically active amine hydrochloride salt (+)-**6** in a simple three-step sequence.[28]

In summary, we have developed a catalytic C–H arylation process for the formation of complex heteroaryl ketones via the combination of diaryliodonium salts and NHC catalysis. The process operates under mild conditions, involves simple experimental protocols, uses a commercially available NHC catalyst, and encompasses a range of high-value heterocyclic systems. We therefore believe that this method will be appealing to practitioners of medicinal chemistry. Studies of the mechanism of the process, including the aryl transfer selectivity, as well as the application of diaryliodonium salts in other catalytic systems are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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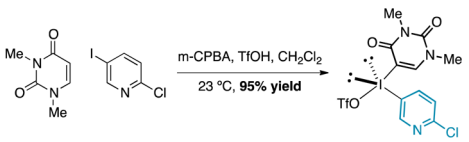

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