

N-Heterocyclic Carbene-Catalyzed Olefination of Aldehydes with Vinyliodonium Salts To Generate α,β -Unsaturated Ketones

Adam A. Rajkiewicz^{†,‡} and Marcin Kalek^{*,†}

[†]Centre of New Technologies, University of Warsaw, Banacha 2C, 02-097 Warsaw, Poland [‡]Faculty of Chemistry, University of Warsaw, Pasteura 1, 02-093 Warsaw, Poland

(5) Supporting Information

ABSTRACT: An organocatalyzed metal-free, direct olefination of aldehydes with vinyliodonium salts has been achieved by an *N*-heterocyclic carbene-promoted C–H bond activation. The reaction proceeds under very mild conditions, delivering a range of (hetero)aryl-vinyl ketones in good yields. The retention of the double bond configuration is uniformly observed, and the application of 2-methoxyphenyl auxiliary group in iodonium salts secures a complete selectivity of the vinyl transfer.

 α,β -Unsaturated ketones constitute a privileged group of reagents in organic chemistry. The overwhelming numbers of their synthetic applications include such landmark processes as a Michael addition,¹ Diels–Alder reaction,² and Morita–Baylis– Hillman reaction.³ This class of compounds is also well represented among natural products and pharmaceutically important molecules.⁴

Not surprisingly, a plethora of synthetic routes have been developed for the preparation of the vinyl ketone moiety.⁵ However, there exist only a handful methods wherein the α,β -unsaturated ketones are obtained by the simplest logical disconnection, that is, by a direct olefination of the C–H bond of aldehydes. The most explored in this context are the transition metal-catalyzed hydroacylations of alkynes, proceeding by the activation of the formyl C–H bond via an oxidative addition to the metal center (eq 1).⁶ In 2013, Lei and co-workers reported an



alternative strategy that relies on a homolytic cleavage of the C–H bond using copper catalyst in the presence of hydroperoxide, effecting an oxidative coupling of aldehydes and alkenes (eq 2).⁷



Herein, we describe our work on a novel, metal-free, direct olefination of aldehydes employing organocatalysis with *N*-heterocyclic carbenes (NHCs) to activate the formyl C–H bond by the formation of Breslow intermediate.⁸ We hypothesized that this nucleophilic species may undergo a reaction with vinyl(aryl)-iodonium salts, which would serve as the donor of the vinyl group (eq 3). An analogous reactivity of the Breslow intermediate toward diaryliodonium salts has been previously described by Gaunt and co-workers.⁹

Vinyl(aryl)iodonium salts have recently become an increasingly important class of electrophilic vinyl transfer reagents.¹⁰ Under noncatalytic conditions, they have been predominantly used for the olefination of heteroatom nucleophiles.¹¹ However, only isolated examples of direct reactions with carbon nucleophiles exist.¹² In the majority of cases, the application of a transition metal catalyst, typically Cu or Pd, has been required to achieve such transformations.¹³ Thereby, the organocatalysis with NHC would establish a metal-free alternative for the vinyl transfer using vinyliodonium salts, resulting in a C–C bond formation.

We started our investigations by examining the reaction between a model aldehyde 1a and phenyl(styryl)iodonium triflate 2a, under the conditions described previously for the coupling of diaryliodonium salts,⁹ i.e., using *N*-pentafluorophenyl-triazolium carbene precursor NHC-1, 4-(dimethylamino)pyridine (DMAP) as the base, and CH_2Cl_2/i -PrOH solvent mixture at -40 °C. We were pleased to see that already this initial attempt resulted in the formation of the desired product 3a, however, accompanied by an approximately equal amount of ketone 3a', originating from the transfer of the aryl group of iodonium salt 2a (Table 1, entry 1). Such behavior is somewhat unusual for vinyl(aryl)iodonium salts since in practically all of their applications reported so far, the

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Table 1. Evaluation of Auxiliary Aryl Groups^a



^{*a*}All data are the average of two experiments. ^{*b*}Determined through analysis by ¹H NMR spectroscopy.

exclusive transfer of the vinyl group has been observed.¹⁴ To address this apparent selectivity issue, we synthesized¹⁵ and evaluated several aryl(styryl)iodonium salts, bearing differently substituted aryl moieties (Table 1). Thus, the presence of sterically hindered and electron-rich aryl groups promotes a highly selective vinyl transfer (entries 2–5), whereas electrondeficient aryl ligands lead to poor selectivities (entries 6–8).¹⁶ 2-Methoxyphenyl is identified as the most efficient auxiliary aryl, securing the formation of vinyl ketone **3a** in 81% yield (entry 4).¹⁷ The observed trends in the reaction selectivity are in a good agreement with the results of studies on unsymmetric diaryliodonium salts, which tend to donate the less bulky and more electron-poor of the two aryl groups.¹⁸ Importantly, all the reactions in Table 1 proceed uniformly with a complete retention of the double bond configuration; no trace of the (Z)-configured

product was detected in any case.¹ Having established the optimal structure of the auxiliary aryl group, we proceeded to the refinement of other reaction parameters. For the model coupling between aldehyde 1a and vinyliodonium salt 2d, we have been able to develop conditions that provide further improvement in the yield of the desired product (Table 2, entry 1). The commercially available Npentafluorophenyl-triazolium carbene precursor NHC-1 proved to be a superior catalyst, whereas related species, NHC-2-NHC-6, do not furnish satisfactory results (entries 2-6). This result is consistent with N-C₆F₅-substituted triazolium NHCs being effective catalysts in the reactions involving Breslow intermediates.^{8,20} Also, no reaction is observed in the absence of the catalyst (entry 7). Elevation of the temperature to 0 °C has a detrimental effect on the efficiency of the coupling (entry 8). Solvent screening disclosed that, while the addition of small amount of *i*-PrOH is beneficial when using CH_2Cl_2 (entries 9 vs 10), if the reaction is performed in DCE alone, a slightly better yield is

 Table 2. Effect of Reaction Parameters^{a,b}

Ç	C X standard conditions:			, Ö
	L _H Ph	NHC-1 (10	mol %)	Me_N_Ph
)_s	——————————————————————————————————————	DMAP (1.5 DCF (0	5 equiv)	Ś
Me 1a	2d (X = TfO)	–35 °C,	24 h	Me 3a
	(1.1 equiv)			
entry	change from the sta	ndard cond	litions	yield (%) ^c
1	none			85
2	NHC-2, instead of I	NHC-1		13
3	NHC-3, instead of NHC-1			5
4	NHC-4, instead of I	NHC-1		71
5	NHC-5, instead of I	NHC-1		<1
6	NHC-6, instead of I	NHC-1		<1
7	no NHC-1			<1
8	0 °C, instead of –35	°C		48
9	CH ₂ Cl ₂ , instead of I	OCE		73
10	CH_2Cl_2/i -PrOH (1	2:1) , instea	ad of D	CE 81
11	DABCO, instead of	DMAP		43^d
12	DIPEA, instead of I	DMAP		54^d
13	Cs ₂ CO ₃ , instead of I	DMAP		26^d
14	$X = BF_4(2i)$, instea	d of X = Tf	0	<1
15	$X = CF_3CO_2(2j)$, in	nstead of X	= TfO	47
16	X = TsO(2k), inste	ad of X = T	ſſO	52
17	X = F(2l), instead of	of X = TfO		77
		⊖ BF₄	\setminus /	ci [©] ci [©]
N N → N → Ph	└─N <mark>N~</mark> Mes	N ≫®-TCIP	S S (⊕)	∠ ^{Ph} Mes ^{-N} √ ^N →Mes
NHC-2	NHC-3	NHC-4	NHC	-5 NHC-6

"Results of further screening of the reaction parameters are given in the SI. ^bAll data are the average of two experiments. ^cDetermined through analysis by ¹H NMR spectroscopy. ^dMinor amount of side product 3a' was observed. Mes = 2,4,6-trimethylphenyl. TCIP = 2,4,6trichlorophenyl.

obtained. Application of bases other than DMAP leads to a considerable decrease in the amount of product, in part due to the emergence of ketone 3a' (entries 11–13). Finally, we evaluated the effect exerted on the reaction outcome by a counterion present in the iodonium salt. It is found that tetrafluoroborate salt is completely ineffective as a donor of the vinyl group (entry 14). The more strongly coordinating ions, namely, trifluoroacetate, tosylate, and fluoride give moderately to slightly lower yields, compared to triflate (entries 15-17).²¹

With the optimized conditions in hand, we set out to explore the scope of the reaction. A range of heterocyclic aldehydes, containing both five- and six-membered rings, are olefinated, producing heteroaryl-vinyl ketones in good yields (Scheme 1, 3a-3f). Substituted benzaldehydes are found to be more challenging substrates, requiring the presence of an electronwithdrawing group in the phenyl ring for the yields to be acceptable (3g-3i).²² Notably, a propargyl aldehyde can also be used as the starting material, furnishing synthetically versatile enynone scaffold (3j). Finally, we applied the developed protocol for the preparation of a pharmaceutically relevant ketone 3k in 39% yield.²³ As far as the limitations are concerned, aliphatic aldehydes are not efficient substrates for the olefination under the developed conditions.

We have also examined the scope with regard to the vinyliodonium salt (Scheme 2). The olefination proceeds in





Scheme 2. Scope with Regard to the Vinyliodonium Salt



synthetically useful yields for an array of β -styryl groups (31–3q). In particular, sterically hindered 2,6-dimethylphenyl moiety (3m), as well as fluorinated and perfluorinated aryls can be incorporated into the product (3p–4q). The electronic properties of the vinyl group seem to have an impact on the efficiency of the reaction; the electron-deficient groups are transferred more effectively than the electron-rich ones. A thiophene functional unit in the β -position of the double bond is also tolerated (3r). Noteworthy, β , β -disubstituted vinyls undergo a transfer under the developed conditions, albeit in somewhat lower yields (3s–3t). Unfortunately, none of the tested iodonium salts with an α -substituted vinyl moiety yielded the desired product, showing that extensive steric hindrance close to the reaction center impedes the coupling. Finally, for β -alkyl-substituted vinyliodonium salts,

irrespective of the choice of the auxiliary aryl group and the salt counterion, the olefination is outcompeted by the undesired aryl transfer (see the Supporting Information for details).

We endeavored to gain some insight into the mechanism of the developed transformation by performing kinetic investigations. The reaction is found to be very rapid at the outset, reaching over 30% yield within the first 5 min (Figure 1, black squares). This



Figure 1. Time-course of the NHC-catalyzed olefination of aldehyde **1f** with salt **2d**: under standard conditions (black squares); with product **3f** (0.3 equiv) added from the outset (blue circles); and with DMAP·TfOH (0.3 equiv) added from the outset (red triangles). The inset shows the first 30 min period in detail.

demonstrates a very high propensity of Breslow intermediate for reacting with vinyliodonium salt. Unfortunately, the fast rate precludes quantitative initial rate measurements using standard techniques.²⁴ Interestingly, the reaction subsequently abruptly decelerates, and it takes several hours to reach a full conversion of the substrate. To probe for a possible inhibition of the reaction by one of its products, we carried out the NHC-catalyzed olefination with either ketone **3f** or DMAP·TfOH added from the outset. The obtained time-course profiles (Figure 1, blue circles and red triangles, respectively) do not differ, within the experimental error, from the one acquired under the standard conditions. We thus speculate that the decrease in the rate is rather due to an unidentified catalyst decomposition pathway.

In conclusion, we have developed an NHC-catalyzed direct ole fination of aldehydes using vinyliodonium salts. The reaction proceeds under very mild conditions and delivers a range of α,β -unsaturated ketones, in particular, those containing pharmacophoric heteroaryl moieties. A careful optimization of the auxiliary substituent of the vinyliodonium salt has allowed for a selective and efficient vinyl transfer to a carbon nucleophile. We believe that this finding has the potential to turn vinyliodonium salts into broadly applicable and robust vinyl transfer reagents under metalfree conditions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00447.

Results of additional investigations, experimental procedures, analytical data, and copies of NMR spectra for products 3a-3t(PDF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: m.kalek@cent.uw.edu.pl.

ORCID 💿

Marcin Kalek: 0000-0002-1595-9818

Notes

The authors declare no competing financial interest.

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