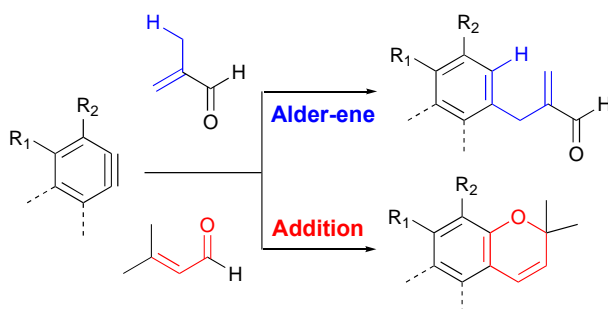


Reactivity of Arynes toward Functionalized Alkenes: Intermolecular Alder-Ene vs. Addition Reactions

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Supporting Information Placeholder



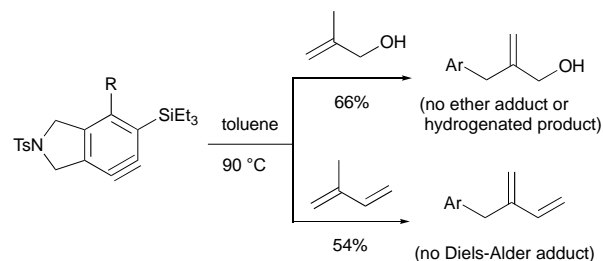
ABSTRACT: The selectivity between two different manifolds of reactions of arynes reacting with functionalized alkenes is described. Arynes generated from bis-1,3-diynes react with various trisubstituted and 1,1-disubstituted alkenes including methallyl amine, prenyl azide, and methacrylic acid, provide mainly addition products of the polar heteroatom functionalities over the Alder-ene products of the alkene segment. The selectivity, however, intricately depends on the substituent pattern of the alkene. Except for the most reactive 2-propenyl group-containing aldehyde, α,β -unsaturated aldehydes generally participated in an addition reaction, generating chromene derivatives.

Alder-ene reactions are an effective functionalization method for allylic C–H bonds with a concomitant 1,3-transposition of the involved alkenes.^{1,2} Due to the broad utility, we investigated the intramolecular Alder-ene reactions of alkene-tethered arynes,³ which can be generated by the hexadehydro Diels-Alder reaction⁴ of tetraynes. The aryne-mediated Alder-ene reactions were further extended to intermolecular versions, where they favorably compete with the addition reaction of lone-pair electrons and π -systems of polar functional groups. For example, both methallyl alcohol and isoprene generated the corresponding Alder-ene product devoid of an ether adduct, hydrogenated product, or a Diels-Alder adduct (Scheme 1).⁵

In order to expand the scope and utility of aryne-based transformations, obtaining comprehensive information about the reactivity of arynes with structurally diverse alkenes containing a heteroatom functionality would be desirable. Thus, we explored the intermolecular Alder-ene reaction of arynes with alkenes⁶ containing a polar functional group such as amine, azide, and carboxylic acid and aldehyde. It was found that the addition reaction of these alkenes generally outcompeted the Alder-ene reaction (Table 1). The aryne generated from symmetrical tetrayne **1** reacted with *N*-methallyl piperidine, affording only deallylated piperidine adduct **3a** in 62% yield (entry 1). On the other hand, *N*-

methallyl morpholine afforded both Alder-ene product **2b** and morpholine adduct

Scheme 1. Competition of the Intermolecular Alder-ene reaction of arynes with addition reactions

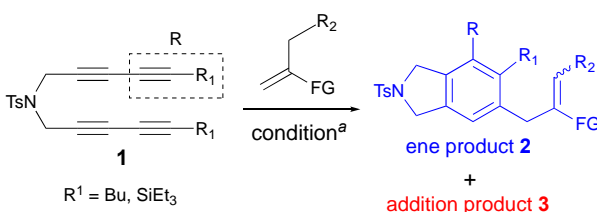


3b in a 1:3 ratio (entry 2). The difference in the product distribution between these two reactions is probably the consequence of the small nucleophilicity difference of the nitrogen center. The reaction of prenyl azide (3:1 isomeric mixture) generated cycloadduct **3c** derived from a primary azide in 76% yield and a trace amount of its regioisomer (entry 3). Methacrylic acid provided a mixture of both ene-product **2d** (33%) and addition product **3d** (40%) (entry 4). While the reaction with methacrolein afforded exclusively Alder-ene product **2e**, the corresponding butyl-substituted

aldehyde generated a 1:1 mixture of Alder-ene product **2f** and *2H*-chromene⁷ derivative **3f** (entry 5).

A proposed mechanism for the formation of *2H*-chromene is shown in Scheme 2.⁸ The overall sequence of events is initiated by the association of the formyl group with an electrophilic aryne moiety to form zwitterionic intermediate **I-1**, which can be further stabilized another resonance form **I-2**. Ring closure of intermediate **I-1** to form oxacyclobutene **I-3** followed by its cycloreversion will generate **I-4**. Finally, the *Z*-isomer of **I-4** undergoes 6π -electrocyclization to generate *2H*-chromene **3** while the *E*-isomer reverts back to **I-4**. The DFT calculated energy profiles corroborate the facile nature of this reaction pathway (see Supporting Information).⁹

Table 1. Alder-ene reactions of functionalized alkenes with an aryne

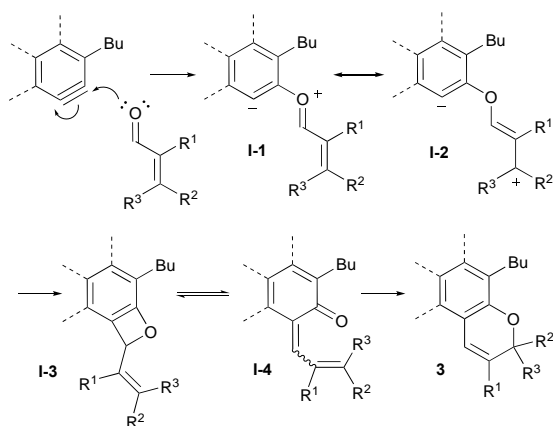
			
entry	alkene	yield of 2 (%) ^b	yield of 3 (%) ^b
1		2a (0)	3a (62)
2		2b (15)	3b (45)
3		2c (0)	3c (76)
4		2d (33)	3d (40)
5		2e (55)	3e (0)
6		2f (23)	3f (23)

^a Alkene (5 equiv), toluene 90 °C, 4 h; ^b Isolated yield

Having seen the change of product distribution caused by the slight structural change in the reacting aldehydes, we further explored the generality of the reaction by employing structurally diversified α,β -unsaturated aldehydes (Table 2). While mono- and disubstituted acrolein such as crotonaldehyde and tiglic aldehyde efficiently generated *2H*-chromenes **3g** and **3h** (entries 1 and 2), β,β -dimethyl acrolein afforded the highest yield of product **3i** (entry 3). Also, the reaction

involving hexa-2,4-dienal afforded **3j** in excellent yield probably due to the development a bisallylic carbocationic character when the initial adduct formed in the reaction pathway (entry 4). The reactions involving cycloalkenyl carboxaldehydes are similar to that of α,β -dimethyl acrolein, generating **3k** and **3l** in 56% and 62% yield, respectively (entries 5 and 6). Because cycloalkylidenyl carboxaldehydes have the same substituent pattern as that of β,β -dimethyl acrolein spirocyclic products **3m–3o** were generated in good yields (entries 7–9).¹⁰

Scheme 2. Proposed mechanism for the reaction of an aryne with an α,β -unsaturated aldehyde to form *2H*-chromene

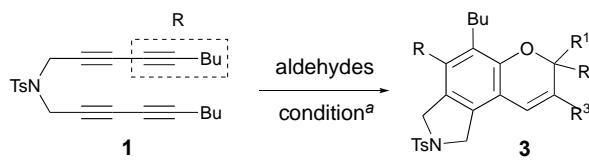
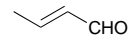
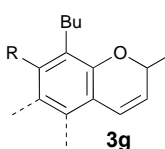
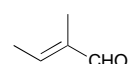
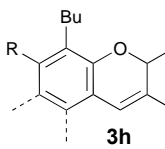
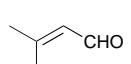
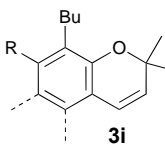
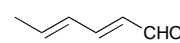
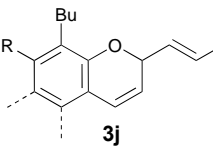
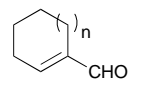
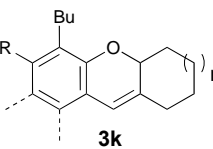
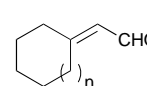
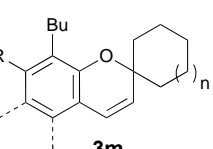


From these reactions, a general trend has emerged: α,β -unsaturated aldehydes undergo an addition reaction most favorably to generate *2H*-chromene derivatives (**3g–3o**) and the efficiency of the reaction decreases with the α -alkyl substituent whereas it increases with the β -alkyl substituent. This trend can be correlated with the stabilizing effect of the developing β -carbocationic character by the β -alkyl substituent¹¹ in intermediate **I-2** in Scheme 2. On the other hand, the α -alkyl substituent may increase the steric hindrance of the aldehyde when it interacts with an aryne counterpart during the conversion of **I-2** to **I-3**.

With the reactivity trend of simple α,β -unsaturated aldehydes in hand, we next examined the reactions of structurally more elaborated α,β -unsaturated aldehydes (Table 3). Perillylaldehyde containing a 4-isopropenyl group on cyclohexenyl carboxaldehyde provided both the Alder-ene product **2p** and the aldehyde addition product **3p** in 24% and 34% yield, respectively (entry 1). On the other hand, β -methyl cyclopentenyl carboxaldehyde with a β,β -dialkyl substituent pattern afforded exclusively the addition product **3q** in 55% yield (entry 2) where the isopropenyl group remained unchanged. The different product distribution from these two aldehydes clearly reflects the aforementioned general trend of aldehyde reactivity. The substituent pattern of geranial also correlates with the general reactivity trend, exclusively providing **3r** in 62% yield without an Alder-ene product (entry 3). Similarly, the citronellal-derived dialdehyde afforded product **3s** (46%) wherein the α,β -unsaturated aldehyde moiety solely participated in the reaction and the saturated aldehyde portion remained intact (entry 4). Finally, dialdehyde containing an α - and a β -methyl substituent afforded chromene **3t** (72%) through the participation of only the β -methyl substituted α,β -unsaturated aldehyde moiety (entry 5).

To diversify the pool of carbonyl groups that can react with arynes, other electron-rich carbonyl compounds were also examined (Table 4). As expected the reactions of aldehyde with no possibility of Alder-ene reaction such as acrolein and 4-dimethylaminocinnamaldehyde afforded 2*H*-chromene derivatives **3u** and **3v** in good yields (entries 1 and 2).

Table 2. Reaction of α,β -unsaturated aldehydes with an aryne to generate 2*H*-chromenes

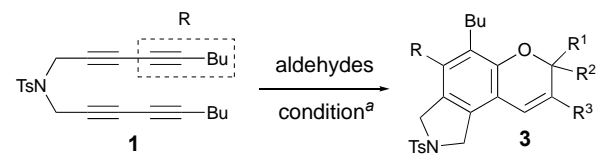
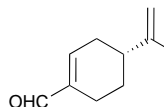
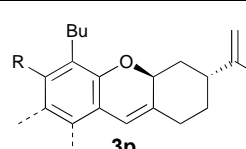
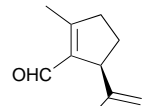
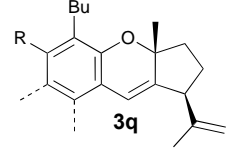
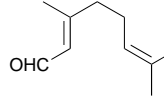
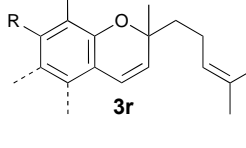
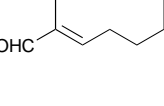
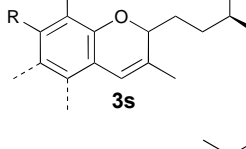
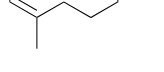
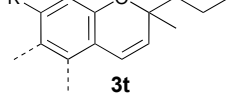
			
entry	aldehydes	2 <i>H</i> -chromene 3	yield (%) ^b
1			71
2			65
3			86
4			84
			
5	n = 0	3k	56
6	n = 1	3l	62
			
7	n = 1	3m	75
8	n = 2	3n	65
9	n = 7	3o	68

^a Alkene (5 equiv), toluene 90 °C, 4 h; ^b Isolated yield.

The reaction with β -diethylaminocinnamaldehyde afforded **3x**, which is the consequence of hydrolysis of the initially formed amino-substituted product during purification on silica gel (entry 3). A β -alkoxy-substituted enal afforded 5,6-spiroketal derivative **3y** in excellent yield (entry 4).¹² Dimethylacrylamide and the corresponding thioamide¹³ also par-

ticipated in the reaction to generate chroman-4-one **3za** and thiochroman-4-one¹⁴ **3zb** in 56% and 51% yield, respectively (entries 5 and 6). An aryne species generated from ester-tethered triyne also reacts with β,β -dimethyl acrolein to afford **3aa** in excellent yield (entry 7). Interestingly, a benzyne generated from trimethylsilylphenyl trifluoromethanesulfonate¹⁵ by treating with CsF participated in the reaction with perillylaldehyde via an Alder-ene manifold to afford **2pa** (75%) without forming

Table 3. The selectivity between the Alder-ene and addition reaction of structurally elaborated aldehydes

			
entry	aldehydes	2 <i>H</i> -chromene 3	yield (%) ^b
1			34 ^c
2			55
3			62
4			46
5			72

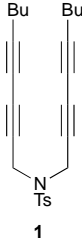
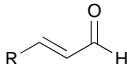
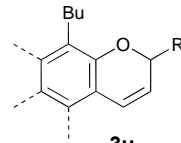
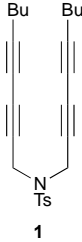
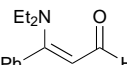
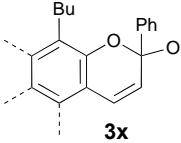
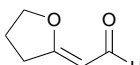
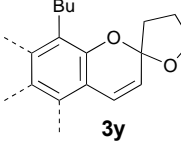
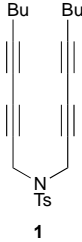
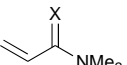
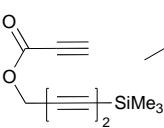
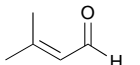
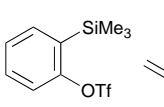
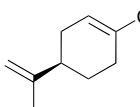
^a Alkene (5 equiv), toluene 90 °C, 4 h; ^b Isolated yield; ^c Ene reaction with the isoprenyl group occurred to generate **2p** in 24% yield.

2*H*-chromene derivatives (entry 8). This is in sharp contrast to the reactivity of the aryne species generated from tetrayne **1** via the hexadehydro Diels-Alder reaction, which preferentially engaged in the reaction with the same aldehyde to generate 2*H*-chromene derivatives **3p** as the major product and Alder-ene product **2p** as the minor product (entry 1 in Table 3).

To gain further insight into the reactivity and selectivity of arynes in different manifolds of reactions, we carried out

DFT calculations (Scheme 3).⁹ As a representative reaction, we used the reaction between the aryne generated from symmetric tetrayne **1** and α,β -unsaturated tiglic aldehyde (Scheme 3). In the calculations, the transition state energies of competing Alder-ene and aldehyde addition reaction were compared. The Alder-ene reaction proceeds through a single transition state **TS1** (11.7 kcal/mol) to generate final ene reaction product (−67.0 kcal/mol). On the other hand, the aldehyde addition occurs via a multiple-step process, where the first transition state **TS2** (4.5 kcal/mol) leads to an intermediate **I-2** (1.2 kcal/mol) (1.2 kcal/mol).

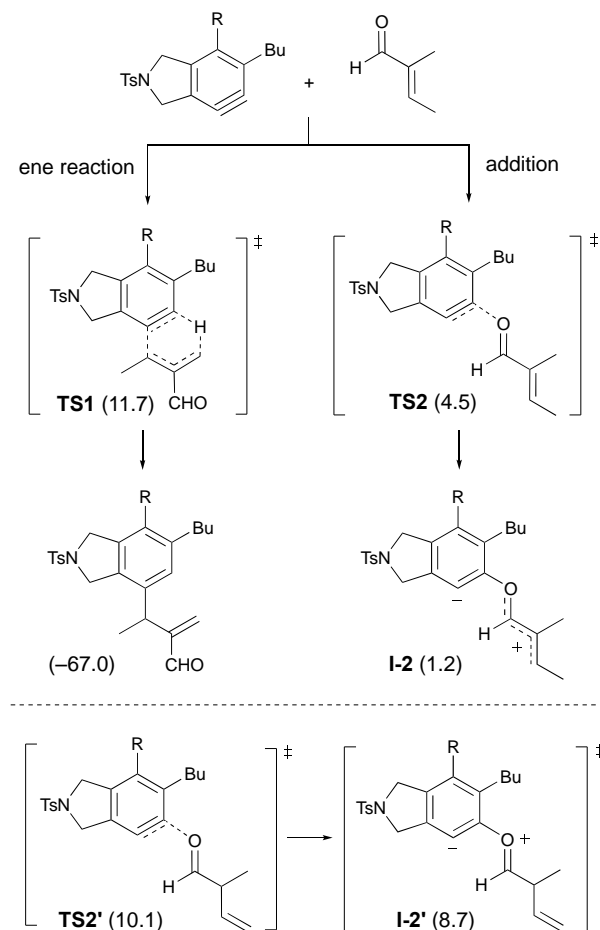
Table 4. Reactivity of electron-rich aldehydes with different arynes

entry	aryne precursor	alkene ^a	product	yield (%) ^b
1				72
2		R = 4-Me ₂ NPh	3v	74
3				54
4				92
5			3za	56
6		X = S	3zb	51
7			3aa	86
8			2pa	75

^a Alkene (5 equiv), toluene 90 °C, 4 h; ^b Isolated yield

These calculated results clearly show that the interaction of the lone pair electrons of the aldehyde with the aryne is kinetically much more favorable to generate the relatively unstable zwitterionic intermediate compared to the abstraction of the allylic hydrogen to form the final Alder-ene product. For the reaction of β,γ -unsaturated aldehyde, the energy of transition state **TS2'** is higher than **TS2** by 5.6 kcal/mol, which corroborates the lack of the reactivity of saturated aldehydes towards the addition reaction to form oxacyclobutenes.

Scheme 3. DFT calculations for the reaction between an aryne and tiglic aldehyde and its deconjugated form



In summary, we have explored the reactions of arynes with functionalized alkenes focusing on the selectivity between Alder-ene and addition reaction manifolds. The reactions of 1,1-disubstituted alkenes containing a polar functional group such as methallyl amine, prenyl azide, and methacrylic acid, provide addition products of the polar heteroatom functionalities predominantly over the Alder-ene reaction of the alkene moiety. The selectivity trend, however, intricately depends on the substituent patterns of the alkene moiety. The addition reaction of α,β -unsaturated aldehyde is generally much more favorable and efficient than Alder-ene reaction. Except for 2-propenyl group-containing aldehyde such as methacrolein, all α,β -unsaturated aldehydes examined in this study preferentially participated in the addition

reaction of the formyl group to generate *2H*-chromene derivatives in high yields. DFT calculations show that the preferred mode of addition of α,β -unsaturated aldehyde is a kinetically favorable process compared to the corresponding Alder-ene reaction. Other electron-rich carbonyl compounds such as dimethyl acrylamide and acrythioamide also participated in the addition reaction to generate chroman-4-one and thiochroman-4-one. It was observed that the structure of arynes and the method of their generation as well, have a significant impact on the reactivity and selectivity between different manifolds of reactions. This implies that the species in the reaction medium including the reagents used for the formation of arylene intermediates and their by-products are not innocent spectators but they may alter the reactivity of arynes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures, characterization data, ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Financial Support from NSF (1361620, DL), Tacoma Technology, and NSFC (2137278 and 21572163, YX) and the mass spectrometry facility at UIUC is greatly acknowledged.

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