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Alder-ene reaction of aryne with olefins

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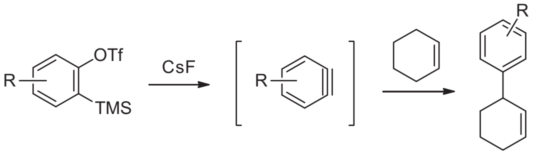
ABSTRACT

A novel intermolecular Alder-ene reaction based on aryne and olefins was developed. We performed this transformation under mild conditions such as at room temperature, and this reaction displayed high selectivity and good yields only in the presence of CsF. Hence, the intermolecular Alder-ene reaction of aryne with olefins provides an effective route to synthesize derivatives of olefins.

Olefins and derivatives of olefins play a very important role in the synthesis of functional organic molecules.[1–4] The substituted allylarenes as one type of key synthetic intermediate have been widely applied in the synthesis of biological drugs, natural products and functional molecules.[5–7] Therefore, the exploration of efficient strategies and methods to synthesize the allylarenes has been an important topic. At present, some approaches have been reported to synthesize the allylarene derivatives such as Friedel–Crafts allylation, Heck coupling reaction of olefins with aryl halides, metal-mediated allylation of aryl nucleophiles, metal-promoted cross coupling reaction of aryl halides with allyl nucleophiles, and selective cross-coupling of organic halides with allylic acetates.[8] Although these methods could efficiently synthesize allylarenes and some functional derivatives, they usually suffer from the expensive metal catalysts and higher temperature. Hence, the development of a simple and mild reaction condition and economic reaction is still significant and a challenging project.

Arynes are highly reactive intermediates,[9] and have been comprehensively utilized as building blocks in organic synthesis.[10] However, the rigorous reaction conditions for their preparation greatly limited their application. With the emergence of moderate preparation methods of arynes,[11] they have attracted considerable attentions in the field of synthetic application. Alder-ene reaction is a kind of classic reaction to construct the carbon–carbon bonds.[12] Many reports based on Alder-ene reaction have been published until now.



Scheme 1. The intermolecular ene reaction of aryne with olefins.

However, there are a few examples of aryne ene reactions, for instance, the intramolecular aryne ene reactions[13–15] and the intermolecular ene reaction of aryne and alkynes.[16] To the best of our knowledge, the intermolecular ene reaction of aryne with olefins is still rather rare so far. Therefore, we were quite curious to clear the situation of the reaction of olefin and aryne. Herein, we report one type of intermolecular aryne ene reaction providing a straightforward access to some allylarene derivatives under mild reaction conditions such as at room temperature, and this synthetic approach also revealed high selectivity and good yields. More importantly, this method is a catalyst-free reaction only in the presence of CsF, moreover, it also displays a wide scope of substrates.

As shown in Scheme 1, the benzyne was formed using the 2-(trimethylsilyl)phenyl trifluoromethanesulfonate as a starting material in the presence of CsF, which was subjected to Alder-ene reaction with olefins to generate allylarene. In the initial studies, *o*-(trimethylsilyl)phenyl triflate **1a** and cyclohexene **1b** were selected as substrates of model reaction in the presence of CsF. In consideration of the easy formation of benzyne in CH_3CN, we firstly investigated this reaction under the condition of 1.0 equiv **1a**, 1.0 equiv **1b**, and 1.0 equiv CsF at 25 °C in anhydrous acetonitrile

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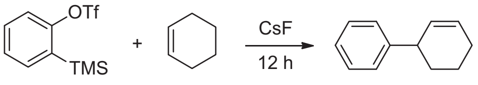
Table 1
Optimization of the intermolecular aryne ene reaction of olefins[a]

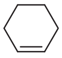
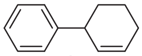
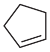
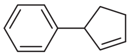
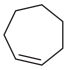
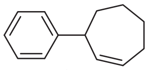
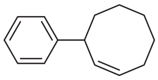
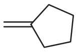
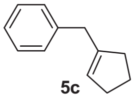
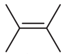
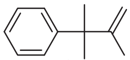
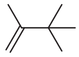
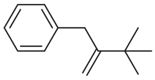
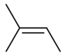
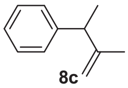
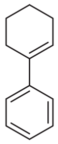
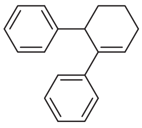
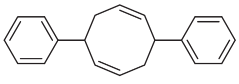


1a **1b** **1c**

Entry	Molar ratio of **1a**/**1b**/CsF	Temp (°C)	Solvent	**1c** yield [b] (%)
1	1/1/1	25	CH_3CN	25
2	2/1/1	25	CH_3CN	21
3	3/1/1	25	CH_3CN	15
4	1/2/1	25	CH_3CN	28
5	1/3/1	25	CH_3CN	33
6	1/4/1	25	CH_3CN	36
7	1/4/2	25	CH_3CN	56
8	1/4/3	25	CH_3CN	76
9	1/4/4	25	CH_3CN	80
10	1/4/4	25	THF	NR[c]
11	1/4/4	25	DCM	NR[c]
12	1/4/4	25	Dioxane	NR[c]
13	1/4/4	50	CH_3CN	71
14	1/4/4	70	CH_3CN	55
15	1/4/4	90	CH_3CN	50
16	1/4/4	110	CH_3CN	37

[a] Reactions performed on 0.5 mmol scale, 5 mL of the solvent.
[b] Isolated yield.
[c] NR: no reaction.

Table 2
Substrate scope for the intermolecular aryne ene reaction of olefins[a]

Entry	Olefin	Product	Yield[b] (%)
1	 **1b**	 **1c**	80
2	 **2b**	 **2c**	85
3	 **3b**	 **3c**	86
4	 **4b**	 **4c**	77
5	 **5b**	 **5c**	75
6	 **6b**	 **6c**	80
7	 **7b**	 **7c**	73
8	 **8b**	 **8c**	75
9	 **9b**	 **9c**	76
10	 **10b**	 **10c**	88

[a] Reaction conditions: *o*-(trimethylsilyl)aryl triflate (1.0 equiv, 1.0 mmol), olefin (4.0 equiv), CsF (4.0 equiv), CH_3CN, 25 °C, 12 h.
[b] Isolated yields.

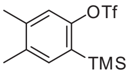
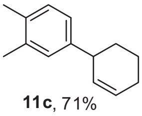
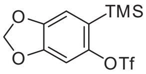
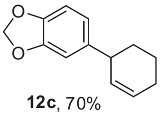
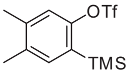
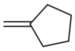
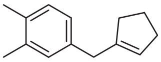
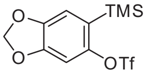
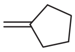
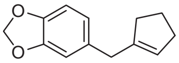
(Table 1, entry (1). Fortunately, the target molecule 3-phenylcyclohexene (**1c**) was obtained in yield of 25%. Subsequently, we tried to change the molar ratio of reactants. As can be observed in Table 1, the decreasing yields were observed along with the increasing of **1a** from 1.0 equiv to 2.0 or 3.0 equiv under the same condition. Simultaneously, a further Aldel-ene reaction between excessive benzyne and product **1c** was observed, to generate more than once ene reaction products. Unfortunately, the reaction system was so intricate that we could not obtain pure multiple ene reaction products. Next, a higher yield (36%) was obtained when the 4.0 equiv cyclohexene was used (Table 1, entries 4–6) compared with entry 1. From these reactions, we found that 1) the amount of benzyne is less than olefins; 2) the amount of cyclohexene can obviously affect the yield of reaction. Subsequently, further investigation was performed by changing the amount of CsF (entries 7–9). An inspiring result that the yields were increasing along with the increasing amount of CsF was observed, and the highest yield of 80% can be afforded when 4.0 equiv were used in this system, which indicated that a large amount of cesium fluoride is indispensable. From these investigations, we found that a 1:4:4 M ratio of the reactants **1a**, **1b**, and cesium fluoride was the best stoichiometric ratio.

Subsequent studies focused on the effects of solvent and temperature. From entries 10–12, the reaction can not work when THF, dichloromethane, and dioxane were utilized as solvents. Meanwhile, we also found that higher temperature will result in the decrease of yields. According to the above studies, the best result (80% yield of 3-phenylcyclohexene **1c**) was obtained by using **1a** (1.0 equiv), 4.0 equiv of **1b**, 4.0 equiv of CsF, 15 mL of acetonitrile at 25 °C for 12 h.

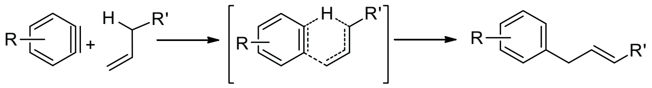
Followed the optimized condition, we then tested the scope of this reaction using a variety of cyclic olefins and alkyl-olefins (Table 2). It was found, except for cyclohexene, substrates of other cyclic olefins, including cyclopentene **2b**, cycloheptene **3b**, and cyclooctene **4b**, could also occur this reaction smoothly in yields ranging from 77% to 86% (entries 2–4). Additionally, under optimized reaction conditions, the substituted chain olefins, including methylene-cyclopentane **5b**, 2,3-dimethyl-2-butene **6b**, 2,3,3-trimethylbutene **7b**, and 2-methyl-2-butene **8b**, were also able to be compatible with this reaction and obtain products with relatively good yields (73–80%, entries 5–8). Besides, 1-phenylcyclohexene **9b**, as a kind of substituted cyclic olefin, exhibited good reactivity and afforded the expected ene reaction product in yield of 76% (entry 9). It was worth noting that the perfect regioselectivity was observed with forming only a type of ene reaction product when we used 2-methyl-2-butene **8b** (entry 8) or 1-phenylcyclohexene **9b** (entry 9) as the reaction substrate. Finally, we made use of 1,5-cyclooctadiene **10b**, a type of dialkene, as the substrate to test the reaction, and we were surprised to realize that intermolecular ene reaction occurred at two olefin function groups to provide product **10c** in yield of 88% (entry 10). Furthermore, we still gained the same product **10c** when the benzyne precursor **1a** was excess.

In addition to the *o*-(trimethylsilyl)phenyl triflate **1a**, other substituted aryne precursors could undergo the intermolecular aryne ene reaction of olefins in this methodology favorably as well (Table 3). The 4,5-dimethylbenzyne precursor **2a**, and the 1,3-benzodioxole derivative **3a** have all been examined under our optimal condition. They formed the expected ene reaction products **11c**, **12c**, **13c**, and **14c**, respectively with yields ranging from 70–74%

Table 3
Investigation of different arynes in the intermolecular aryne ene reaction of olefins[a]

Entry	Benzyne	Olefin	Product[b]
1	 **2a**	 **1b**	 **11c**, 71%
2	 **3a**	 **1b**	 **12c**, 70%
3	 **2a**	 **5b**	 **13c**, 73%
4	 **3a**	 **5b**	 **14c**, 74%

[a] Reaction conditions: *o*-(trimethylsilyl)aryl triflate (1.0 equiv, 1.0 mmol), olefin (4.0 equiv), CsF (4.0 equiv.), CH_3CN, 25 °C, 12 h.
[b] Isolated yields.



Scheme 2. The mechanism of intermolecular Alder-ene reaction based on aryne and olefins.

(entries 1–4). The mechanism of ene reaction of aryne with olefins is similar to that of general ene reaction (Scheme 2).

In summary, a significant and selective procedure for the intermolecular ene reaction of aryne with olefins has been developed, and this method has been shown to be tolerant of a wide variety of substituted chain olefins and cyclic olefins with excellent yields under moderate condition of reaction. The work provides an efficient approach for the preparation of some allylarene derivatives.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.049.

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