

Reactivity and Selectivity in the Intermolecular Alder–Ene Reactions of Arynes with Functionalized Alkenes

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(5) Supporting Information

ABSTRACT: The reactivity and selectivity of functionalized alkenes in intermolecular Alder—ene reactions with arynes is described. The arynes generated from bis-1,3-diynes react with various trisubstituted and 1,1-disubstituted alkenes containing hydroxyl, amino, halo, carboxyl, boronate, and 1,3-dienyl functionalities, providing product distributions with varying degrees of selectivity between Alder—ene and addition reactions. The geometry of alkenes is another important



factor for the reactivity of di- and trisubstituted alkenes where the allylic hydrogen of *cis*-disposed alkenyl system is reactive, which is the opposite reactivity compared to the corresponding intramolecular reaction.

A lder–ene reactions are an effective synthetic method to functionalize allylic C–H bonds with a concomitant 1,3transposition of the involved alkenes.¹ A wide variety of electron-deficient π -systems have been employed as ene acceptors for thermal and Lewis acid catalyzed Alder–ene reactions, while alkenes can participate in the reaction if a suitable transition-metal catalyst is used.² Recently, Lee and other groups took advantage of the hexadehydro Diels–Alder reaction as an effective method for generating arynes³ and using them in intramolecular Alder–ene reactions.^{4,5} To expand the scope and utility of the green nature of the Alder–ene reaction requiring no additional reagents other than heat for allylic C–H bond functionalization,⁶ we envision an intermolecular Alder– ene reaction of arynes with alkenes containing an additional functional group (Scheme 1). Although the intermolecular

Scheme 1. Intermolecular Alder-ene Reactions of Arynes



Alder–ene reactions of hydrocarbon-based symmetrical alkenes with structurally simple arynes are reported in the literature,⁷ the reactions of functionalized unsymmetrical alkenes in intermolecular Alder–ene reactions have not been explored. Herein, we describe the characteristic reactivity and selectivity features of intermolecular Alder–ene reactions of functionalized alkenes with arynes generated via hexadehydro Diels– Alder reaction conditions.

First, we examined the Alder-ene reaction by using a symmetrical tetrayne (1) and electronically deactivated ene-

donor methyl methacrylate (Table 1). Reactions with varying amounts of the ene donor showed that 5 equiv of methyl methacrylate relative to the aryne precursor 1 provided the highest yield of the ene reaction product 2a (72%); thus, subsequent studies employed this stoichiometry unless stated otherwise. Under this optimized condition, the Alder–ene





^aAll alkenes are used in 5 equiv amount relative to 1. ^bIsolated yield. ^cWith a larger scale (1 mmol), **2a** was obtained in 68% yield.

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reactions of other 1,1-disubstituted alkenes bearing additional functional groups provided the corresponding Alder–ene products **2b–h** in good yields ranging from 55% to 81%.

Next, we examined the reactivity of trisubstituted alkenes containing a substituent, including an allylic bromide, a conjugated carboxylate, a ketal, dimethyl malonate moiety, a carbamate, an ester, an aldehyde, and a silyl ether (Table 2).





The overall yields of the reaction involving these trisubstituted alkenes (entries 1-7) are slightly lower (ranging from 35 to 65%) than those of 1,1-disubstituted alkenes. It is worth noting that the geometrical isomers show a stark difference in reactivity such that the *E*-isomer generates ene reaction product **3g** (entry 7), but the corresponding *Z*-isomer yields no ene reaction product (entry 8).

The reactivity difference between 1,1-disubstituted and trisubstituted alkenes and the allylic C-H bonds of cis- and *trans*-disposed methyl groups were further examined⁸ (Scheme 2). When methallylprenyl ether was heated with 1, a mixture of 3h and 3i was obtained in 61% yield with a ratio of 1.5:1, which suggests that 1,1-disubstituted alkenes are slightly more reactive than trisubstituted alkenes. The reactivity of geometrical isomers of trisubstituted alkenes was examined with geraniol and nerol. The reaction with geraniol afforded a mixture of 3j (60%) and 3k (27%) in a 2.2:1 ratio. On the other hand, nerol provided only a single Alder-ene product 31 (66%) along with a sizable amount of hydrogenation product 4 (19%). The different product distribution indicates that the allylic C-H bonds on the methyl group cis to the substituent on the next carbon are reactive in the Alder-ene reaction, while the corresponding C-H bonds on the trans methyl group are inert. This is further confirmed by employing a deuterated nerol, which provided product 31-d where deuterium is completely Scheme 2. Reactivity of 1,1-Di- and Trisubstituted Alkenes and Geometrical Isomers of Trisubstituted Alkenes



retained in the methyl group. The transition-state energies from DFT calculations⁹ (Scheme 2) are consistent with this conclusion. The Alder–ene reaction with a *trans*-disposed methyl group leads to a transition state higher in energy by 3.4 kcal/mol than that of the *cis*-disposed methyl group. This is because the *trans*-disposed methyl group becomes a pseudoe-quatorial substituent at the transition state, which develops an extra nonbonded interaction against the aryne moiety.

With the relative reactivity trend of differently substituted alkenes in hand, we next examined the reaction profiles of alkenyl alcohols (Table 3). In general, disubstituted alkenes containing a hydroxyl group provide only hydrogenation¹⁰ product 4 (entries 1-4). Upon converting the hydroxyl group to a silyl ether moiety, the cis- alkene became reactive for an ene reaction (cyclooctadiene mono epoxide in entry 4) but the trans-alkene was unreactive (TBS ether of crotyl alcohol in entry 1). Trisubstituted alkenyl alcohols generated varying degree of the Alder-ene reaction and hydrogenation depending on the disposition of allylic C-H bonds. For example, verbenol afforded only hydrogenation product because of the unreactive *trans*-disposed methyl group (entry 5), while prenyl alcohol and 6-methylhept-5-en-2-ol provided mainly Alder-ene products 5f and 5g along with 4 (entries 6 and 7). 1,1-Disubstituted alkenyl 1° and 2° alcohols provided exclusively Alder-ene products **5h**-**j** (entries 8–10) except for an alkene containing an allylic 2° hydroxyl group, which promotes hydrogenation, forming 4 in significant amount (entry 11). A notable observation from Table 3 is the lack of aryl ethers albeit alcohols can undergo addition with arynes easily.

Recognizing the preferred Alder-ene reactivity of an aryne, we next examined the competition between an Alder-ene and a Diels-Alder reaction¹¹ by employing alkenes containing a 1,3-diene moiety (Table 4). Acyclic dienes such as isoprene and 2,3-dimethylbutadiene provided only Alder-ene products **6a** and **6b** in 54% and 58% yield, respectively (entries 1 and 2), while the pivalate-substituted 2,3-dimethylbutadiene afforded a

Table 3. Ene Reactions of Alkenyl Alcohols with an Aryne



^{*a*}Alkene (5 equiv), toluene 90 °C, 4 h. ^{*b*}Isolated yield. ^{*c*}The reaction led to polymerization of the aryne intermediate. ^{*d*}The reaction provided Alder–ene product **5d**' in 52% yield. ^{*e*}Even with 5 equiv each of MeOH and methallyl alcohol, only an Alder–ene reaction occurred without formation of MeOH adduct.

Table 4. Selectivity between an Alder–Ene and Diels–Alder Reaction of 1,3-Dienes Reacting with an Aryne



1:1 mixture of **6c** and Diels–Alder product **7c** in 52% overall yield (entry 3). From cyclic dienes such as furan and pyrrole

regardless of the tethered alkene, only Diels–Alder reaction products 7d-f were obtained in good yields (entries 4–6).

Finally, we examined the regioselectivity (ortho/meta) of the Alder–ene reaction with other unsymmetrical arynes (Table 5).

Table 5. Regioselectivity in the Alder–Ene Reaction of Arynes



The reaction of an NTs-tethered symmetrical tetrayne and methyl methacrylate afforded isoindolines 8a-c and 2d in good yields where the ratio of *ortho/meta* changes from 1.4:1 (H) to only meta (SiEt₃) depending on the steric bulk of the substituent. On the other hand, the reaction of an ynamidetethered tetrayne afforded the ortho-isomer of indolines 9a-c with Bu, H, and an aryl substituent on the aryne but generated only the *meta*-isomer 9d with SiEt₃ substituent. The aryne with a fluorenone skeleton showed substituent-dependent ortho/ meta selectivity where a sterically less hindered butyl group afforded a 1.4:1 mixture of 10-ortho and 10-meta, whereas a bulky SiEt₃ group confer an excellent control to generate only meta product 10b. Similar selectivity was observed for metaisomers of 11 and 12. It is worth noting that the general regioselectivity in the Alder-ene products 8, 10, 11, and 12 is opposite to that of other nucleophile additions.¹² Only indolines 9a-c showed the same preference of a meta isomer in both Alder-ene reaction and other nucleophile addition reactions.

In summary, we have systematically investigated the reactivity and selectivity issues of the Alder-ene reactions of arynes reacting with a variety of alkenes containing additional functional groups. In general, 1,1-disubstituted acyclic and cyclic alkenes are most favorable for Alder-ene reaction over other reactions such as hydrogenation by hydrogen transfer from an alcohol moiety or its direct addition to form aryl ethers. The reactivities of trisubstituted alkenes are slightly lower than 1,1-disubstituted alkenes, and the disposition of the reacting allylic C-H bonds is crucial for their reactivity: the allylic C-H bonds of the carbon cis to the substituent on the next carbon are reactive but the corresponding C-H bonds on the trans position are inert. For acyclic 1,3-dienes containing allylic C-H bonds, an Alder-ene reaction is more favorable over a Diels-Alder reaction. On the other hand, alkenetethered cyclic dienes such as furan and pyrrole participate in Diels-Alder reactions much more favorably over an Alder-ene process because of the alkene moiety. High regioselectivity in Alder-ene reactions has been demonstrated by judiciously installing substituents with steric and electronic factors. Overall, the aryne-mediated Alder-ene reaction is an effective and

green protocol for allylic C–H functionalization that has its own merit compared to other methods.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.7b02438.

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

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Notes

The authors declare no competing financial interest.

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