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

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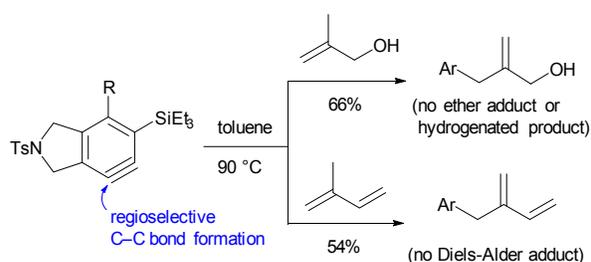
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The selectivity between two different manifolds of reactions of arynes reacting with functionalized alkenes is described. Arynes generated from bis-1,3-diynes react with various trisubstituted and 1,1-disubstituted alkenes including methallyl amine, prenyl azide, and methacrylic acid, providing 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.

Scheme 1. Intermolecular Alder-ene reactions of arynes outcompeting addition reactions

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 reaction[4] 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 alkenes containing a polar functional group[6] such as amine, azide, 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

ene product **2b** and morpholine adduct **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).[7] 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 2*H*-chromene[8] derivative **3f** (entry 5 and 6).

A proposed mechanism for the formation of 2*H*-chromene is shown in Scheme 2.[8,9] 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 **1-1** 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 2*H*-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).[10]

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Table 1. Alder-ene reactions of arynes with functionalized alkenes

entry	alkene	yield of **2** (%)[b]	yield of **3** (%)[b]
1	X = CH$_2$	**2a** (0)	**3a** (62)
2	X = O	**2b** (15)	**3b** (45)
3	(4:1)[c]	**2c** (0)	**3c** (76)[d]
4		**2d** (33)	**3d** (40)
5	R = H	**2e** (55)[e]	**3e** (0)
6	R = C$_4$H$_9$	**2f** (23)[f]	**3f** (23)

[a]Tetrayne **1** (20–50 mg), alkene (5 equiv), toluene 90 °C, 4 h; [b]Isolated yield; [c]1-Azido-3-methylbut-2-ene and 3-azido-3-methylbut-1-ene exist in a 4:1 equilibrium ratio; [d]10:1 regioisomers [d]5:1 regioisomers; [e]10:1 regioisomeric mixture.
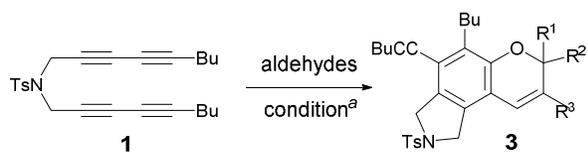
Having seen the change of product distribution caused by the slight structural change in the reacting aldehydes, we further explored the generality of the reaction by employing structurally diversified α,β-unsaturated aldehydes (Table 2). While mono- and disubstituted acrolein such as crotonaldehyde 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).[11]
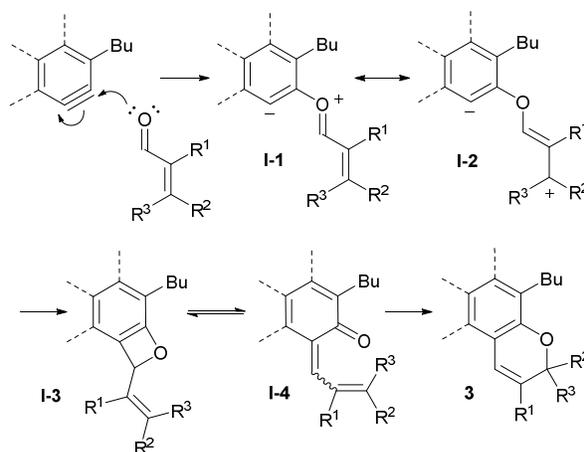
Scheme 2. Proposed mechanism for the reaction of an aryne with an α,β-unsaturated aldehyde to form 2H-chromene

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 substituent[12] 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 unreacted. 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).
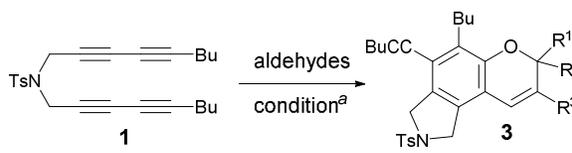
To diversify the pool of carbonyl groups that can react with arynes, other electron-rich carbonyl compounds were also examined (Table 4). As expected the reactions of aldehyde with no possibility of Alder-ene reaction such as acrolein and 4-dimethylaminocinnamaldehyde afforded 2H-chromene derivatives **3u** and **3v** in good yields (entries 1 and 2). The reaction with β-diethylaminocinnamaldehyde afforded **3x,** which is the

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

entry	aldehydes	*2H*-chromene 3	yield (%)[b]
1	OHC (crotonaldehyde)	**3g**	71
2	OHC (methacrolein/tiglaldehyde)	**3h**	65
3	OHC (β,β-dimethylacrolein)	**3i**	86
4	OHC (sorbaldehyde)	**3j**	84
5	OHC ( )n, n = 0	**3k**	56
6	n = 1	**3l**	62
7	OHC ( )n, n = 1	**3m**	75
8	n = 2	**3n**	65
9	n = 7	**3o**	68

[a]Tetrayne **1** (20–50 mg), alkene (5 equiv), toluene 90 °C. [b]Isolated yield.

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).[13] Dimethylacrylamide and the corresponding thioamide[14] also participated in the reaction to generate chroman-4-one **3za** and thiochroman-4-one[15] **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, the benzyne generated from 1-trimethylsilyl-2-phenyl triflates with fluoride[16] or from aprotic diazotization of anthranilic followed by thermal decomposition of the diazonium carboxylate in the presence of
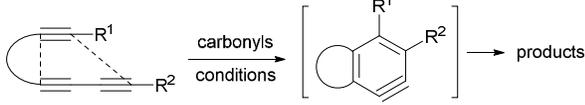
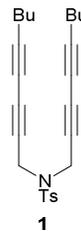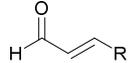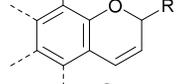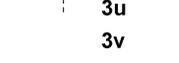**Table 3.** The selectivity between Alder-ene and addition reactions of structurally elaborated aldehydes

entry	aldehydes	*2H*-chromene 3	yield (%)[b]
1	OHC (4-isopropenylcyclohexene carbaldehyde)	**3p**	34[c]
2	OHC (cyclopentene carbaldehyde)	**3q**	55
3	OHC (citral-type)	**3r**	62
4	OHC / OHC	**3s**	46[d]
5	CHO / CHO	**3t**	72

[a]Tetrayne **1** (20–50 mg), alkene (5 equiv), toluene 90 °C. [b] Isolated yield. [c]Ene reaction product (**2p**) with the isoprenyl group was also obtained in 24% yield. [d]For easier purification, the crude product was treated with NaBH₄ and the corresponding alcohol was isolated and oxidized to **3s** with yield referring to final isolated yield.

perillylaldehyde afford only the Alder-ene product **2pa** in 75% and 42% yield without forming *2H*-chromene derivative (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 *2H*-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 different manifolds of reactions with arynes, 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

Table 4. Reactivity of α,β-unsaturated aldehydes and electron-rich carbonyl compounds with arynes

entry	aryne precursor	alkene[a]	product	yield (%)[b]
1	**1**	R = H	**3u**	72
2		R = 4-Me$_2$NPh	**3v**	74
3			**3x**	54
4			**3y**	92
5		X = O	**3za**	56
6		X = S	**3zb**	51
7			**3aa**	86
8			**2pa**[c]	75

[a]Tetrayne **1** (20–50 mg), alkene (5 equiv), toluene 90 °C. [b]Isolated yield. [c]Benzyne generated from aprotic diazotization of anthranilic acid afforded **2pa** in 42% yield as a sole product.

first transition state **TS2** (4.5 kcal/mol) leads to an intermediate **I-2** (1.2 kcal/mol). 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.
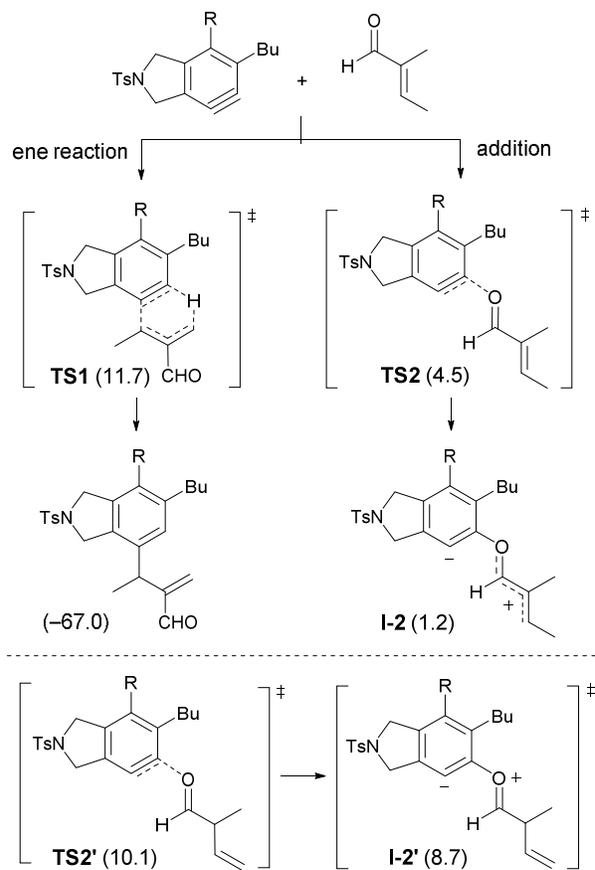
Scheme 3. DFT calculations for the reaction between an aryne and tiglic aldehyde and its deconjugated form

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 2*H*-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 acrylthioamide 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

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that the species in the reaction medium including the reagents used for the formation of aryne intermediates and their byproducts are not innocent spectators but they may alter the reactivity of arynes.

Acknowledgment

Notes and references

(1) For general reviews on Alder-ene reactions: (a) K. Mikami and M. Shimizu, *Chem. Rev.,* 1992, **92**, 1021–1050. (b) L. C. Dias, *Curr. Org. Chem.,* 2000, **4**, 30–342. (c) W. Adams and O. Krebs, *Chem. Rev.,* 2003, **103**, 4131–4146. For a review on transition metal-catalyzed Alder-ene reactions: (d) B. M. Trost, M. U. Frederiksen and M. T. Rudd, *Angew. Chem., Int. Ed.,* 2005, **44**, 6630–6666.

(2) Previous Reports for Alder-ene reactions of arynes: (a) V. Garsky, D. F. Koster and R. T. Arnold, *J. Am. Chem. Soc.*, 1974, **96**, 4207–4210. (b) A. A. Aly, N. K. Mohamed, A. A. Hassan and A. -F. E. Mourad, *Tetrahedron,* 1999, **55**, 1111–1118. (c) A. A. Aly and R. M. Shaker, *Tetrahedron Lett.*, 2005, **46**, 2679–2682. (d) T. T. Jayanth, M. Jeganmohan, S.-M. Cheng and C.-H. Cheng, *J. Am. Chem. Soc.,* 2006, **128**, 2232–2233. (e) Z. Chen, J. Liang, J. Yin, G. A. Yu and S. H. Liu, *Tetrahedron Lett.,* 2013, **54**, 5785–5787. (f) P. Pérez and L. R. Domingo, *Eur. J. Org. Chem.,* 2015, 2826–2834. (g) R. Jin, S. Liu and Y. Lan, *RSC Adv.*, 2015, **5**, 61426–61435.

(3) (a) D. A. Candito, J. Panteleev and M. Lautens, *J. Am. Chem. Soc.*, 2011, **133**, 14200–14203. (b) D. A. Candito, D. Dobrovolsky and M. Lautens, *J. Am. Chem. Soc.,* 2012, **134**, 15572–15580. (c) R. Karmakar, M. Phani, Y. Y. Sang and D. Lee, *Org. Lett.,* 2013, **15**, 1938–1941. (d) D. Niu and T. R. Hoye, *Nat. Chem.,* 2014, **6**, 34–40. (e) J. Zhang, D. Niu, V. A. Brinker and T. R. Hoye, *Org. Lett.,* 2016, **18**, 5596–5599.

(4) (a) A. J. Bradley and R. P. Johnson, *J. Am. Chem. Soc.,* 1997, **119**, 9917–9918. (b) K. Miyawaki, R. Suzuki, T. Kawano and I. Ueda, *Tetrahedron Lett.,* 1997, **38**, 3943–3946. (c) T. R. Hoye, B. Baire, D. Niu, P. H. Willoughby and B. P. Woods, *Nature* 2012, **490**, 208–212. (d) S. Y. Yun, K. P. Wang, N. K. Lee, P. Mamidipalli and D. Lee, *J. Am. Chem. Soc.,* 2013, **135**, 4668–4671. (e) Y. Liang, X. Hong, P. Yu and K. N. Houk, *Org. Lett.,* 2014, **16**, 5702–5705. (f) D. J. Marell, L. R. Furan, B. P. Woods, X. Lei, A. J. Bendelsmith, C. J. Cramer, T. R. Hoye and K. T. Kuwata, *J. Org. Chem.,* 2015, **80**, 11744–11754. (g) R. Karmakar, K. P Wang, S. Y. Yun, P. Mamidipalli and D. Lee, *Org. Biomol. Chem.,* 2016, **14**, 4782–4788. (h) Q. Hu, L. Li, F. Yin, H. Zhang, Y. Hu, B. Liu and Y. Hu, *RSC Adv.,* 2017, **7**, 49810–49816 (i) Y. Hu, J. Ma, L. Li, Q. Ho, S. Lv, B. Liu and S. Wang, *Chem. Commun.*, 2017, **53**, 1542–1545. (j) O. J. Diamond and T. B Marder, *Org. Chem. Front.*, 2017, **4**, 891–910.

(5) S. Gupta, P. Xie, Y. Xia and D. Lee, *Org. Lett.,* 2017, **19**, 5162–5165.

(6) (a) L. Campbell-Verduyn, P. H. Elsinga, L. Mirfeizi, R. A. Dierckx and B, L. Feringa, *Org. Biomol. Chem.,* 2008, **6**, 3461–3463. (b) A. A. Cant, G. H. V. Bertrand, J. L. Henderson, L. Roberts and M. F. Greaney, *Angew. Chem., Int. Ed.*, 2009, **48**, 5199–5202. (c) A. V. Dubrovski and R. C. Larock, *Org. Lett.,* 2010, **12**, 3117–3119. (d) R. Karmakar, S. Y. Yun, K. P. Wang and D. Lee, *Org. Lett.*, 2014, **16**, 6–9. (e) S. S. Bhojgude, A. Bhunia and A. T. Biju, *Acc. Chem. Res.,* 2016, **49**, 1658–1670. (f) S. P. Ross, B. Baire and T. R. Hoye, *Org. Lett.,* 2017, **19**, 5705–5708. (g) S. Ghorai and D. Lee,

Tetrahedron, 2017, **73**, 4062–4069. (h) S. P. Ross and T. R. Hoye, *Org. Lett.,* 2018, **20**, 100–103. (i) T. Roy and A. T. Biju, *Chem. Comm.*, 2018, **54**, 2580–2594.

(7) The regioselectivity for addition product **3d** is opposite to N nucleophiles as in **3a** and **3b**. This is accordance to our previous observation (ref. 6d). For theoretical studies on regioselectivity of aryne reactions: (a) P. H. -Y. Cheong, R. S. Paton, S. M. Bronner, G-Y. J. Im, N. K. Garg and K. N. Houk, *J. Am. Chem. Soc.,* 2010, **132**, 1267–1269. (b) J. M. Medina, J. L. Mackey, N. K. Garg and K. N. Houk, *J. Am. Chem. Soc.* 2014, **136**, 15798–15805.

(8) Reports on the reaction of arynes with α,β-unsaturated aldehydes: (a) H. Heaney and J. M. Jablonski, *Chem. Comm.*, 1968, **18**, 1139. (b) H. Heany, J. M. Jablonski and C. T. McCarty, *J. Chem. Soc., Perkin Trans. 1,* 1972, 2903–2910. (b) A. T. Bowne and R. H. Levin, *Tetrahedron Lett.* 1974, **23**, 2043–2046. (c) T. Zhang, X. Huang and L. Wu, *Eur. J. Org. Chem.,* 2012, 3507–3519. (d) T. Wang and T. R. Hoye, *J. Am. Chem. Soc.,* 2016, **138**, 13870–13873. (e) X. Meng, S, Lv, D. Cheng, Q. Hu, J. Ma, B. Liu and Y. Hu, *Chem. Eur. J.,* 2017, **23**, 6264–6271.

(9) Representative examples of [2+2] cycloaddition of arynes and carbonyl compounds involving oxacyclobutene intermediate: (a) H. Yoshida, M. Watanabe, H. Fukushima, J. Ohshita and A. Kunai, *Org. Lett.,* 2004, **6**, 4049–4051. (b) Y. Eito, S. Kohtani and H. Miyabe, *Org. Lett.,* 2010, **12**, 1956–1959. (c) H. Yoshida, Y. Ito and J. Ohshita, *Chem. Commun.,* 2011, **47**, 8512–8514. (d) E. Yoshioka, S. Kothani and H. Miyabe, *Angew. Chem., Int. Ed.,* 2011, **50**, 6638–6642. (e) Y. Eito and H. Miyabe, *Tetrahedron*, 2012, **68**, 179–189. (f) Y. Eito, S. Kohtani and H. Miyabe, *Molecules*, 2014, **19**, 863–880. (g) H. Miyabe, *Molecules,* 2015, **20**, 12558–12575. (i) Y. Hu, Y. Hu, Q. Hu, J. Ma, S. Lv, B. Liu and S. Wang, *Chem. Eur. J.,* 2017, **23**, 4065–4072.

(10) All calculations are carried using Gaussian 09 suite by MO6/6-311+G(d,p)//B3LYP/6-31+G* in a toluene dispersed phase. Energies for all intermediates and transition states have been calculated and provided in the Supporting Information. Probable structures of the transition states are also provided.

(11) T. Wang, C. J. Oswood and T. R. Hoye, *Synlett*, 2017, **28**, A-C.

(12) G. Desimoni and G. Tacconi, *Chem. Rev.*, 1975, **75**, 651–692.

(13) Reports on synthesis of [5,6]-spiroketals: (a) C. C. Lindsey, L. K. Wu and T. R. R. Pettus, *Org. Lett.,* 2006, **8**, 2365–2367. (b) M. A. Marsini, Y. Huang, C. C. Lindsey, K.-L. Wu and T. R. R. Pettus, *Org. Lett.*, 2008, **10**, 1477–1480. (b) G. Zhou, J. Zhu, J. Xie and Y. Li, *Org. Lett.*, 2008, **10**, 721–724. (c) M. A. Brimble, M. C. McLeod, Z. E. Wilson, D. C. K. Rathwell and T.-Y. Yien, *Pure Appl. Chem.* 2012, **84**, 1379–1390.

(14) V. Palani, J. Chen and T. R. Hoye, *Org. Lett.* 2016, **18**, 6312–6315.

(15) (a) M. Fridén-Saxin, T. Seifert, M. R. Landergren, T. Suuronen, M. Lahtela-kakkonen, E. M. Jarho and K. J. Luthman, *Med. Chem.,* 2012, **55**, 7104–7113. (b) C. Conti, L. P. Monaco and D. Desideri, *Bioorg. Med. Chem.*, 2011, **19**, 7357–7364.

(16) (a) Y. Himeshima, T. Sonada and H. Kobayashi, *Chem. Lett.,* 1983, **12**, 1211–1214. (b) S. Liu, Y. Li and Y. Lan, *Eur. J. Org. Chem.,* 2017, 6349–6353.