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Intramolecular Aryne−Ene Reaction: Synthetic and Mechanistic Studies

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Supporting Information

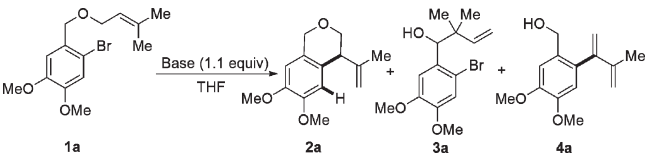
ABSTRACT: Although the chemistry of arynes is well developed, some challenges still remain. The ene reaction of arynes has not gained widespread use in synthesis as a result of poor yields and selectivity. A general, high yielding and selective intramolecular aryne−ene reaction is described providing various benzofused carbo- and heterocycles. Mechanistic data is presented, and a rationale for the resulting stereochemistry is discussed.

Arynes are among the first reactive intermediates known to organic chemists. Since their discovery, they have fascinated chemists from both theoretical and synthetic perspectives. These remarkable intermediates possess a wide reactivity profile, engaging in pericyclic reactions, nucleophilic addition, and transition metal-mediated/catalyzed reactions.[1] In spite of their intrinsically high reactivity, many synthetically useful processes have been developed. However, certain challenges still remain such as the aryne−ene reaction and Diels−Alder reactions of acyclic dienes.[2a]

The aryne−ene reaction, although well-known, has not enjoyed widespread use in synthesis, primarily due to poor selectivity (competing [2 + 2] or [4 + 2] cycloaddition, regioselectivity) and low yields.[3] Only a few isolated examples of efficient aryne−ene reactions have been reported, with a noteworthy example being the intermolecular reaction of arynes and alkynes reported by Cheng and co-workers.[3b] We were interested to see whether we could control the outcome of the reaction by tethering the olefin to the aryne precursor. Doing so would allow for the use of deprotonation-based methods of aryne generation, thereby simplifying the starting materials employed and providing an interesting annulation strategy.[4] Herein we report the development of a general, high yielding, and selective intramolecular aryne−ene reaction providing straightforward access to benzofused carbo- and heterocycles.

Initial experiments began with substrate **1a** at very high dilution in order to minimize any potential intermolecular reactions with the base or substrate (Table 1, entry 1). The reaction was found to be very sluggish; however, we were pleased to see that **1a** had cleanly converted to **2a**. Increasing the concentration steadily increased the conversion and yield (entries 1−3) and adding the base at room temperature further improved the conversion (entry 4). When 2 equiv of LDA was added at the beginning of the reaction, **2a** reacted further to form product **4a**, which likely arose from deprotonation at the benzylic position of **2a** and subsequent ring-opening (entry 5). Other lithium amide bases were also investigated; LiHMDS did not lead to any conversion, and KHMDS was a competent base but did not prove advantageous (entries 6 and 7). Interestingly LiTMP and $Me_2Zn(TMP)Li$[5] gave mixtures of **2a** and **3a**, where the latter likely arises by deprotonation of **1a** at the benzylic position and subsequent [2,3]-Wittig rearrangement.

Table 1. Optimization of Intramolecular Aryne−Ene Reaction[a]



1a 2a 3a 4a

entry	base	conc (M)	conv[b] (%)	**2a**[b] (%)	**3a** (%)	**4a** (%)
1[c,e]	LDA	0.003	23	23[d]		
2[c]	LDA	0.012	54	52		
3[c]	LDA	0.024	64	63		
4	LDA	0.024	100	88[d]		<5
5[f]	LDA	0.024	100	54		40[d]
6	LiHMDS	0.024	<5			
7	KHMDS	0.024	80	67		
8	LiTMP	0.024	77	39	38[d]	
9	$Me_2Zn(TMP)Li$	0.024	51	23	28[d]	

[a] Reaction conditions: **1a** (1 equiv, 1 mmol), base (1.1 equiv), THF, rt, 24 h. [b] Determined by NMR using mesitylene as an internal standard. [c] Lithium amide added at −78 °C using syringe pump, then rt, 24 h. [d] Isolated yield. [e] 48 h. [f] LDA (2 equiv). LDA = lithium diisopropylamide, LiHMDS = lithium bis(trimethylsilyl)amide, LiTMP = lithium tetramethylpiperidide.

The proposed mechanism of this reaction is depicted in Scheme 1. Base induced elimination generates the aryne intermediate, which then engages in an ene reaction with the pendant olefin. It is generally believed that the aryne−ene reaction takes place in a concerted manner; however, a mechanism involving radical intermediates has also been proposed.[3] The results of DFT calculations performed at the B3LYP/6-31G* level of theory revealed an early transition state having a chairlike conformation (Scheme 1).[6] The transition state was found to be concerted but asynchronous, with C−C bond formation being more advanced. The process may resemble the nucleophilic attack of the electron-rich olefin onto the in-plane π-bond of the aryne.[7] Inspection of hand-held and computational models revealed that the

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Scheme 1. Intramolecular Aryne−Ene Reaction

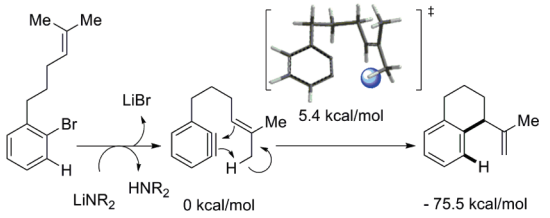
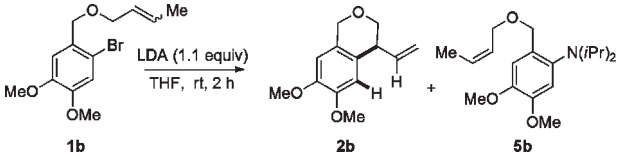


Table 2. Reactions of *cis*- and *trans*-1b[a]

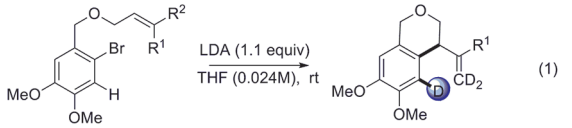


	1b	ratio *cis*/*trans*	conv[b] (%)	product ratio[b] (2b/5b)	yield (%)[c]
1	*trans*-1b	6:94	79	94:6	69
2	*cis*-1b	98:2	84	2:98	73

[a] Reaction conditions: **1b** (1 equiv, 0.5 mmol), LDA (1.1 equiv), THF (0.024 M), rt, 2 h. [b] Determined by ^{1}H NMR on crude reaction mixture. [c] Combined isolated yield.

trans-allylic-H should be transferred preferentially (Scheme 1, highlighted). All attempts to find a transition state where the *cis*-allylic-H migrated collapsed to the transition state for the migration of the *trans*-allylic-H.

Reaction of deuterium labeled substrate **1a-d_6** led to complete transfer of deuterium (eq 1), consistent with a unimolecular concerted process. In the case of substrate **1a-d_3**, complete deuterium transfer was also observed, which confirmed the preference for the *trans*-allylic-H to migrate and further reinforced the notion that no intermediates are formed in this reaction.



(1)

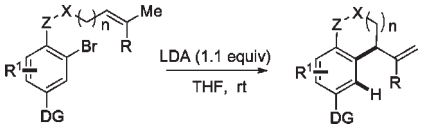
1a-d_6: $R^1 = R^2 = CD_3$, > 95% D
1a-d_3: $R^1 = CH_3$, $R^2 = CD_3$, 91:9 *E*:*Z*

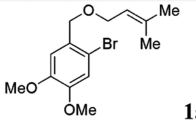
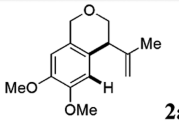
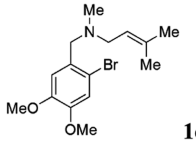
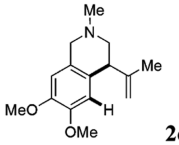
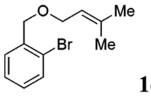
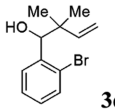
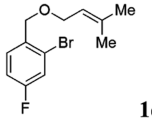
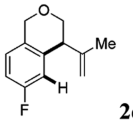
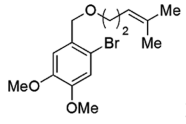
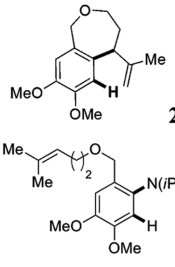
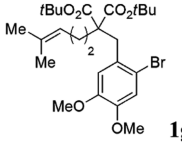
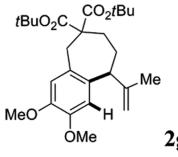
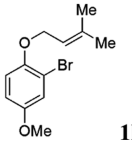
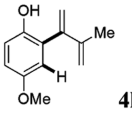
2a-d_6: $R^1 = CD_3$, 89% yield, > 95% D
2a-d_3: R^1 = Me, 89% yield, 93% D

We were intrigued by the complete and selective deuterium transfer from **1a-d_3** to form **2a-d_3** and wondered what effect olefin geometry had on reactivity. The reactions of *cis*- and *trans*-**1b** displayed marked differences (Table 2). *trans*-**1b** reacted to give **2b** as the major product (entry 1), whereas *cis*-**1b** reacted to give **5b** as the major product. The isomeric ratio of the starting material is reflected in the product distribution, revealing that the ene reaction of *cis*-**1b** is too slow and outcompeted by the intermolecular reaction of the aryne intermediate with an external nucleophile. Thus, the geometry of the olefin is an important factor in determining the success of this reaction with *cis*-olefins being unsuitable reaction partners.

With a set of suitable conditions in hand we went on to explore the scope of this transformation (Table 3). Initially, we were interested in replacing the oxygen atom in the chain with a nitrogen

Table 3. Intramolecular Aryne−Ene Reaction[a]



Entry	Substrate	Product(s)	Yield (%)[b]
1	 **1a**	 **2a**	89
2[c]	 **1c**	 **2c**	89
3	 **1d**	 **3d**	61
4	 **1e**	 **2e**	65
5	 **1f**	 **2f** **5f**	95 (1.7:1)[d]
6[e]	 **1g**	 **2g**	90
7[f]	 **1h**	 **4h**	89

[a] Reaction conditions: **1** (1 equiv, 0.5 mmol), LDA (1.1 equiv), THF (0.024 M), rt, 24 h. [b] Isolated yields. [c] THF (0.05 M). [d] Ratio of **5f**/**2f**. [e] LDA (1.1 eqiuv), THF (0.05 M), rt, 1.5 h, then LDA (0.5 equiv), 0.5 h. [f] LDA (2.2 equiv), THF (0.024 M), rt, 1.5 h.

atom. The reaction of **1c** was more sluggish than that of **1a**, and a higher concentration was necessary for full conversion (entry 2). The reaction of substrate **1d** under standard conditions yielded **3d**

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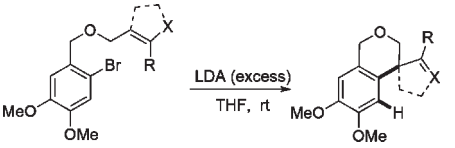
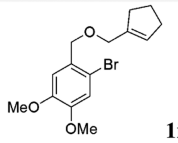
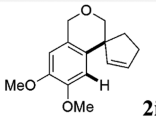
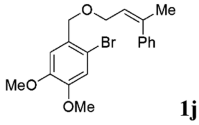
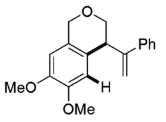
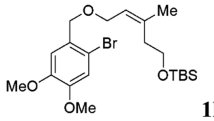
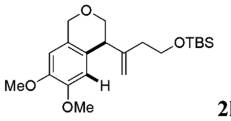
Table 4. Intramolecular Aryne−Ene Reaction

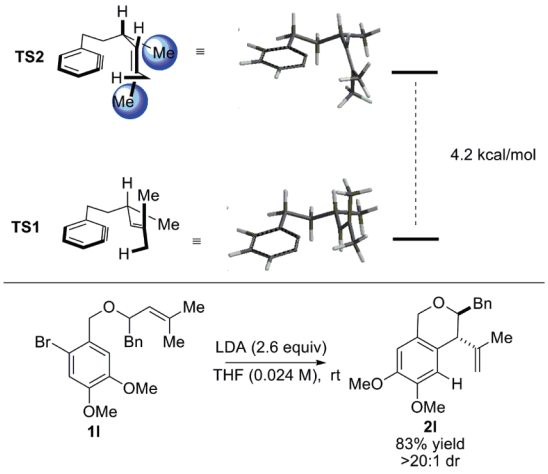


	Substrate	Product	Yield (%)[d]
1[a]	 **1i**	 **2i**	76
2[b]	 **1j** 14:1 *Z*:*E*	 **2j**	81
3[c]	 **1k**	 **2k**	82

[a] Reaction conditions: **1i** (1 equiv, 0.5 mmol), LDA (1.1 equiv), THF (0.024 M), rt, 24 h. [b] Reaction conditions: **1j** (1 equiv, 0.25 mmol), LDA (1.1 equiv), THF (0.1 M), rt, 3 h, then LDA (1.1 equiv), 1 h. [c] Reaction conditions: **1k** (1 equiv, 0.25 mmol), LDA (1.1 equiv), THF (0.1 M), rt, 3 h, then LDA (1.1 equiv), 1 h, then LDA (0.1 equiv), 0.25 h. [d] Isolated yields.

in 61% yield (entry 3). In this case deprotonation takes place at the benzylic position and [2,3]-Wittig rearrangement occurs, as was previously observed. This result suggests that a directing group is necessary in a 1,3-relationship to the bromine. The two groups act in concert, leading to selective deprotonation.[8] A fluorine atom was a suitable directing group; in this case, it is conceivable that the fluorine or bromine could be eliminated to produce different arynes; however, **1e** eliminates selectively and ultimately provides **2e** as the only product in 65% yield (entry 4). We then sought to determine the effect of ring size on the efficiency of the reaction (entries 5−7). Substrate **1f** reacted to give a mixture of the desired cyclized product, **2f**, and product **5f**, resulting from competing intermolecular attack of the base (entry 5). Substrate **1g** reacted sluggishly; however, the reaction could be pushed to completion at higher concentration with the addition of more LDA. In the case of substrate **1h**, under standard conditions, none of the desired cyclized product could be observed; however, its formation could be inferred from the ring opened product **4h**. An excellent yield of **4h** could be obtained by using 2.2 equiv of LDA. In this case, ring-opening takes place very readily due to the better leaving group ability of a phenolate. Furthermore, the strain of the five-membered ring may contribute to the facile ring-opening. We then examined the effect of substitution on the olefinic portion of our substrates (Table 4). Substrate **1i** reacted smoothly to provide spirocyclic compound **2i**, bearing an all carbon quaternary center (entry 1). Substrate **1j** was obtained as an inseparable mixture of *Z*/*E* isomers but reacted smoothly to provide **2j**. The power of this methodology is demonstrated in the reaction of substrate **1k**; in this case, the *trans*-allylic-H is exclusively transferred to provide a single regioisomer. The analogous transition metal-catalyzed Heck reaction would be expected to be nonselective or selective for the more substituted double bond.

Scheme 2. Stereoselective Intramolecular Aryne−Ene Reaction



We were interested in the prospect of a stereoselective substrate-controlled aryne−ene reaction (Scheme 2). DFT calculations were performed on a model substrate bearing a methyl substituent in order to determine the feasibility of a stereoselective reaction. Two pseudochairlike transition states, **TS1** and **TS2**, with significantly different energies were found (Scheme 2). The methyl group is placed pseudoequatorially and rotation about the single bond provides access to diastereomer. **TS1** suffers from 1,3-allylic strain arising from an eclipsing interaction of the hydrogen and methyl group; however, **TS2** suffers from a steric interaction with the methyl substituent on the chiral center and the *cis*-allylic methyl group raising its energy 4.2 kcal/mol above **TS1** (Scheme 2, highlighted). An energy difference of this magnitude should result in the observation of a single diastereomer. Treatment of substrate **1l** with LDA (1.1 equiv) at room temperature and stirring for 24 h led to the appearance of a single product; however, starting material remained, and the reaction could be pushed to completion by the periodic addition of more LDA.[9] **1l** reacted smoothly to provide **2l** exclusively as the *trans*-isomer in excellent yield. The activation energy barrier for reaction is close to the differences in energy between different conformers of the starting material; because of this, the observed selectivity likely reflects the conformational preferences of the starting materials.[10]

In conclusion, we have described a general, high yielding, and highly stereo- and regioselective aryne−ene reaction. Tethering of the ene component to the aryne allows for the use of deprotonation-based methods of aryne generation, leading to simplified starting materials, and eliminates competing side reactions. The reaction appears to proceed by an early asynchronous-concerted transition state which allowed for regioselective hydrogen migration. Furthermore, it was found that the transformation is highly stereoselective. The full details of this study will be described in due course.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, computational data, and characterization data for all new compounds.

This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) A simple conformer search was performed using molecular mechanics MMFF and revealed a preference for the *cis*-methyl substituent to eclipse the allylic hydrogen as in **TS1**.