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First synthesis of a highly strained cyclodeca-1,5-diyne skeleton via intramolecular Sonogashira cross-coupling

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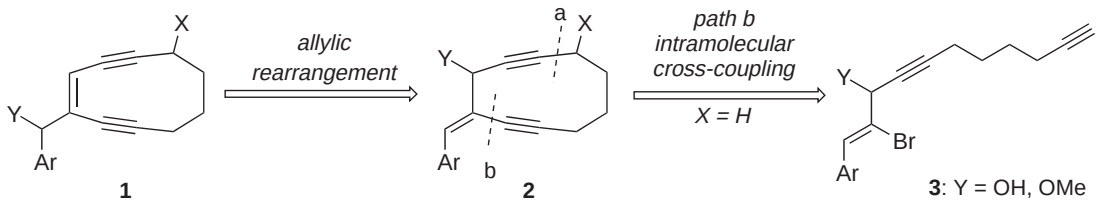
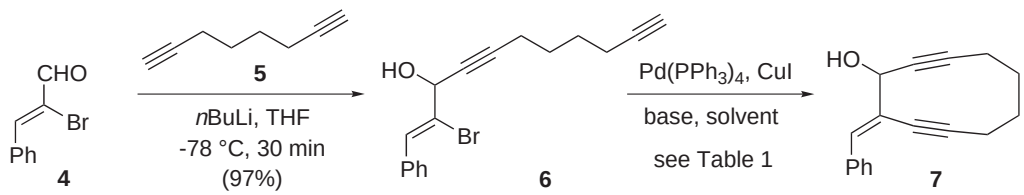
Abstract—Cyclization of alkenyl bromides **6** and **11** containing a terminal alkyne was achieved by using an intramolecular cross-coupling reaction catalyzed by Pd(0) and Cu(I). Under the optimal reaction conditions, cyclodeca-1,5-diyne derivatives **7** and **12** were obtained in 43 and 28% yields, respectively. © 2000 Elsevier Science Ltd. All rights reserved.

The cross-coupling reaction of alkenyl halides or triflates with 1-alkynes under the Sonogashira conditions[1] is a useful method for synthesis of conjugated enynes.[2] However, the formation of medium-size rings directly via the Sonogashira cross-coupling is rare probably due to the bent triple bond that creates unfavorable ring strain. Schreiber et al. reported an elegant synthesis of the dynemicin A skeleton through cross-coupling of an alkenyl bromide with a 1-alkyne to form a 15-membered lactone followed by an intramolecular Diels–Alder reaction.[3] Hirama et al. reported a synthesis of the cyclodeca-1,6-diyne skeleton possessing an exocyclic double bond by using cross-coupling of an alkenyl bromide with activated tributyltin acetylide[4] under the Stille direct coupling conditions.[5] It was found that the same cyclization did not take place between alkenyl bromides and the corresponding 1-alkyne under the Sonogashira conditions.[4a,6] By taking advantage of activation of both cross-coupling partners, 9- or 10-membered 1,5-diyne-3-enes were constructed via reaction of (*Z*)-bis(trimethylstannyl)ethylene with 1,7-diiodo-1,6-heptadiyne or 1,8-diiodo-1,7-octadiyne under the Stille direct coupling conditions.[7] We report here the first example of an intramolecular Sonogashira cross-cou-



Scheme 1.



Scheme 2.

Keywords: coupling reactions; diynes; alkenyl halides; cyclization.

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pling for synthesis of the highly strained cyclodeca-1,5-diyne skeleton.

In our previous study, cyclodeca-1,5-diyne **2** (Ar = Ph, X = anthraquinone-2-carbonyloxy, Y = OH) was transformed into the 10-membered enediyne **1** (Y = EtO) via acid-catalyzed allylic rearrangement.[8] We prepared alcohol **2** (Ar = Ph, X = OH, Y = OTHP) via acetylide addition to an aldehyde in 10% yield along with 20% of the undesired intermolecular addition byproduct (path a in Scheme 1).[8a] In order to improve the efficiency of cyclization, we turned our attention to path b by using an intramolecular cross-coupling of the alkenyl bromide with the 1-alkyne within **3** for construction of **2** with X = H.

Scheme 2[9] illustrates the two-step synthesis of (*E*)-4-(phenylmethylidene)cyclodeca-1,5-diyn-3-ol **7**. Starting from commercially available α-bromocinnamaldehyde **4** and 1,7-octadiyne **5**, alcohol **6** was obtained in 97% yield via mono-deprotonation of **5** by using 1 equiv. of *n*-BuLi followed by addition to aldehyde **4** (Scheme 2). Cyclization of **6** was carried out in the presence of 10 mol% $Pd(PPh_3)_4$ and 20 mol% CuI under high dilution conditions. We systematically examined the effects of amine base, solvent, temperature and reaction time on the yield of **7**. The results are summarized in Table 1. When the cross-coupling reaction was carried out at room temperature (20°C) in neat Et_3N or Et_2NH, no reaction occurred with recovery of **6** (entries 1 and 3). The same reaction run in the presence of a solvent such as THF or CH_3CN at room temperature gave an oxidative coupling byproduct in 25–26% yield, resulting from dimerization of the terminal alkyne moiety in **6** (entries 9 and 10). The same byproduct was formed when the reaction was carried out in refluxing Et_3N (entry 2). Therefore, the 'normal reaction protocol' (Et_3N, THF and room temperature)[8b,e] used for intermolecular cross-coupling failed for cyclization of **6**.

Next, we checked the reaction temperature and time for cyclization of **6** in neat Et_2NH (entries 4–7). At 50–60°C for 2.5 h, the desired product **7** was obtained in 11% yield. The yield of **7** increased to 35% on heating at 80–90°C for 1.5 h. However, prolonged reaction at 50–60°C or at 80–90°C for 4 h led to decomposition of **7**. Addition of THF as the co-solvent for reaction at 50–55°C in entry 8 had a little effect on the yield of **7** (entry 8 versus entry 4). These results indicated that a high temperature (80–90°C) is preferred for cyclization of **6** but the product **7** decomposes spontaneously so that the isolated yield of **7** is time-dependent.

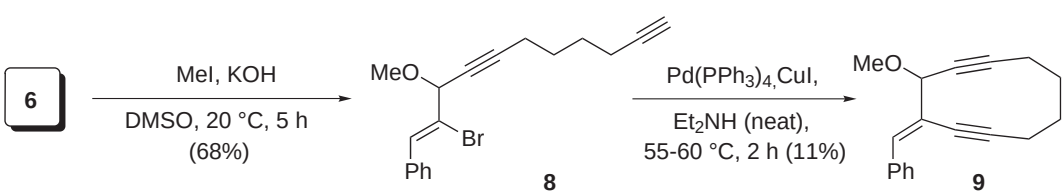
By keeping reaction temperature at 80–90°C for 1.5 h, we optimized the ratio of Et_2NH and CH_3CN (entries 11–14). Reduction of Et_2NH from neat to 25% in CH_3CN improved the yield of **7** from 35 to 41% (entry 6 versus entry 11). The best yield of 43% was obtained when a 1:5 mixture of Et_2NH and CH_3CN was used (entry 12). On further dilution to a 1:10 ratio, the yield dropped sharply to 18% (entry 14). Increase in the concentration of **6** from 0.02 to 0.05 M reduced the yield of **7** (entry 13). We also used other secondary and primary amines to replace Et_2NH in the cyclization of **6** under the optimal conditions. All experiments resulted in lower yields of **7** (entries 15–18).

With the success in the cyclization of the alcohol **6** through the intramolecular Sonogashira cross-coupling reaction, we explored cyclization of ether **8** (Scheme 3).[9] Methylation of **6** with MeI and KOH in DMSO gave compound **8** in 68% yield. The latter compound cy-

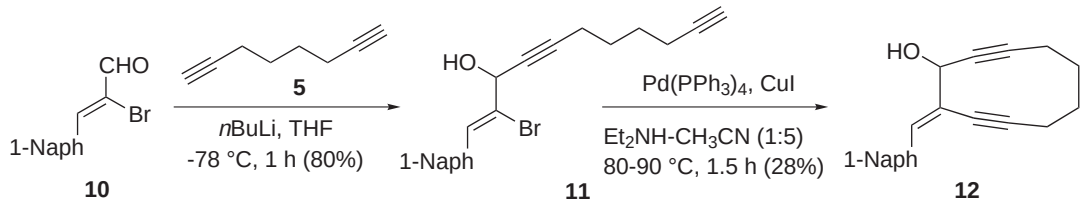
Table 1. Effects of base, solvent, temperature (*T*) and time (*t*) on cyclization of **6** to form **7**[a]

Entry	Base, solvent	*T* (°C),[b] *t* (h)	**7** (%)	Entry	Base, solvent	*T* (°C),[b] *t* (h)	**7** (%)
1	Et_3N (neat)	20, 24	0	10	Et_2NH–CH_3CN (1:3)	20, 10	(25)[d]
2	Et_3N (neat)	90, 1	(26)[d]	11	Et_2NH–CH_3CN (1:3)	80–90, 1.5	41
3	Et_2NH (neat)	20, 48	0	12	Et_2NH–CH_3CN (1:5)	80–90, 1.5	43
4	Et_2NH (neat)	50–60, 2.5	11	13	Et_2NH–CH_3CN (1:5)[c]	80–90, 1.5	28
5	Et_2NH (neat)	50–60, 4	(Dec.)	14	Et_2NH–CH_3CN (1:10)	80–90, 1.5	18
6	Et_2NH (neat)	80–90, 1.5	35	15	iPr_2NH–CH_3CN (1:3)	80–90, 1.5	12
7	Et_2NH (neat)	80–90, 4	(Dec.)	16	Piperidine–CH_3CN (1:5)	80–90, 1.5	23
8	Et_2NH–THF (1:1)	50–65, 4	9	17	Morpholine–CH_3CN (1:5)	80–90, 1.5	25
9	Et_3N–THF (1:15)	20, 12	(26)[d]	18	$(CH_3O)_2CHCH_2NH_2$–CH_3CN (1:5)	80–90, 1.5	4

[a] The reaction was carried out at 0.02 M of **6** in the presence of 10 mol% $Pd(PPh_3)_4$ and 20 mol% CuI.
[b] Oil bath temperature.
[c] At 0.05 M of **6**.
[d] Yield of oxidative coupling byproduct of terminal alkyne **6**.



Scheme 3.



Scheme 4.

clized, in the presence of 10 mol% $Pd(PPh_3)_4$ and 20 mol% CuI in neat Et_2NH at 55–60°C for 2 h, to give **9** in 11% yield. The lower yield might be due to the methoxy group in **8**, which serves as a better leaving group than the hydroxyl group in **6**. Thus, decomposition through side-reactions of the allylic or propargylic methyl ether with Pd(0)[10] or Pd(II)[11] species generated in the reaction significantly reduced the yield of **9**. This was also true for the corresponding allylic acetate that decomposed entirely on heating in neat Et_2NH.

To expand the intramolecular cross-coupling reaction, we synthesized the 1-naphthyl analogue **12** (Scheme 4).[9] Addition of the mono-lithium acetylide derived from 1,7-octadiyne **5** and *n*-BuLi with **10** provided alcohol **11** in 80% yield. The Pd(0)–Cu(I) catalyzed cyclization of **11** was carried out under the optimal conditions used for **6** to give compound **12** in 28% isolated yield. The diminished yield of **12** compared to **7** may arise from the bulky 1-naphthyl group, which may cause unfavorable steric interaction during the oxidative addition of the alkenyl bromide to the Pd(0) catalyst.

In summary, we have established an intramolecular cross-coupling reaction of alkenyl bromides with 1-alkynes for an expeditious synthesis of the highly strained cyclodeca-1,5-diyne skeleton. Key factors to our success are use of a secondary amine base, a high reaction temperature (80–90°C) and short reaction times. With this intramolecular cross-coupling approach, we synthesized compound **7** in two steps and in 42% overall yield from commercial materials. Moreover, alcohols **7** and **12** are useful precursors for the synthesis of 10-membered enediynes capable of cleaving DNA and inhibiting cancer cell growth.[8a] Application of this cyclization to the synthesis of related compounds is underway in our laboratory.

Acknowledgements

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