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COMMUNICATION

Alkynylation/Dearomatizative Cyclization to Construct Spiro[5.5]undecanes

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A new access to spiro[5.5]undecane frameworks was reported through the $ZnMe_2$-promoted alkynylation of salicylaldehyde and HCO_2H-mediated dearomatizative cyclization that can be used to construct an all-carbon quaternary spirocenter. This method can be applied to the rapid synthesis towards a series of useful motifs of natural products, such as the core of elatol and aphidicolin.

Spirocycles[1] are a common structural pattern found at the core of numerous natural products with broad structural diversities and important bioactivities (Figure 1).[2] For example, elatol displays activity against bacteria (including human pathogenic bacteria)[3a-b] and demonstrates cytotoxicity against HeLa and Hep-2 human carcinoma cell lines.[3c] Aphidicolin also exhibits significant antiviral and antitumor activity.[4a-b]

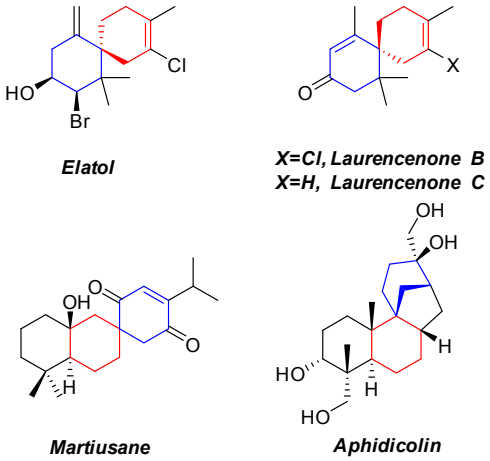

Figure 1. Selected natural products containing spiro[5.5]undecane cores.

One commonly exploited mechanistic approach to construct spirocycle skeleton is the dearomatizative spirocyclization of functionalized phenols and naphthols. For example, chiral hypervalent iodine catalyst using m-CPBA as terminal oxidant was developed for intramolecular spirolactonization.[5,6] Palladium- or iridium-catalyzed intramolecular allylic dearomatization of phenols was also described.[7] Feringa *et al*. developed one-pot spirocyclization involving asymmetric conjugate addition and subsequent oxidative dearomatization of 2-naphthols.[8] Katsuki *et al*. reported iron-catalyzed asymmetric tandem spirocyclization from 1-methyl-2-naphthols and phenols.[9] Luan *et al*. and You *et al*. described Ru or Rh-catalyzed vinylative dearomatization of naphthols or phenols *via* a C(sp^2)–H bond activation approach.[10] Gulías *et al*. and Lam *et al*. independently reported Rh-catalyzed spiroannulation of *ortho*-vinylphenols triggered by terminal C–H functionalization of the alkenyl moiety.[11] Luan *et al*. developed a Pd-catalyzed [2+2+1] annulative dearomatization between β-naphthols and two alkyne units,[12] and Pd-catalyzed alkyne insertion/β-naphthol dearomatization cascade to construct spirocycles.[13] Other methods were also described by various groups.[14-18] However, the reported approaches are either transition-metal catalysis or their substrates are mostly limited to structurally similar cyclic lactones or lactams. Thus, new strategies for intermolecular spirocyclization using different classes of starting materials in one-pot process are highly desirable but challenging.

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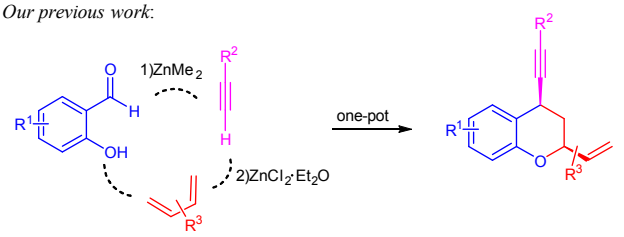
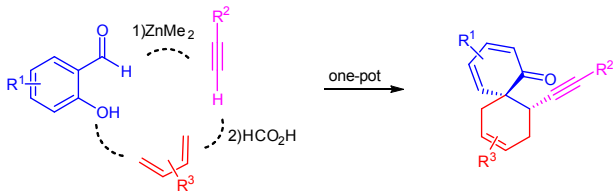
Our previous work:



This work:

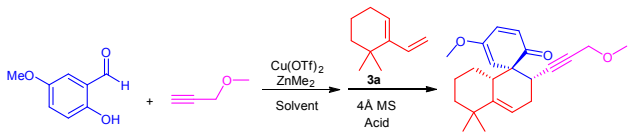


Scheme 1. Alkynylation/cyclization in one-pot process.

In 2015, we reported an approach to synthesize 2,4-difunctionalized benzopyrans in one-pot process (Scheme 1, top).[19] As a continuation of our focus on this research program, the present paper describes a new access to spiro[5.5]undecane frameworks through the $ZnMe_2$-promoted alkynylation of salicylaldehyde and HCO_2H-mediated dearomatizative cyclization that can be applied to construct an all-carbon quaternary spirocenter (Scheme 1, bottom).

The present investigation began by reacting different diene substrate (**3a**) with 5-methoxysalicylaldehyde (**1a**) and 3-methoxyprop-1-yne (**2a**) under standard reaction conditions, which were developed in our previous research.[19] We unexpectedly obtained a spirocycle product (**4a**) in 7% yield instead of benzopyran compound (Table 1, entry 2). The structure of **4a** was identified by X-ray crystallography (Figure 2).

Table 1 Optimization of reaction conditions[a]



1a 2a 4a

Entry[b]	Acid	Solvent	temp (°C)	Yield (%)[c]
1	$BiCl_3$	toluene	40	trace
2	$ZnCl_2·Et_2O$	toluene	40	7
3	CF_3CO_2H	toluene	40	trace
4	MSA	toluene	40	7
5	(R)-(-)-BPA[d]	toluene	40	11
6	p-TsOH	toluene	40	18
7	CSA	toluene	40	32
8	CH_3CO_2H	toluene	40	41
9	HCO_2H	toluene	40	43
10[e]	HCO_2H	toluene	40	39
11[f]	HCO_2H	toluene	40	32
12	HCO_2H	THF	40	trace
13	HCO_2H	Hexane	40	30
14	HCO_2H	CH_2Cl_2	40	25
15	HCO_2H	CH_2Cl_2	r.t.	46

[a]Unless otherwise specified, all reactions were performed using $Cu(OTf)_2$ (8 mol%), $ZnMe_2$ (5 equiv), **1a** (1 equiv), **2a** (4 equiv), **3a** (5 equiv), and acid (1.5 equiv). [b]For all entries, dr is > 20:1, which was determined by ^1H NMR spectroscopy. In our experimental results, if diastereoisomers could not be detected in ^1H NMR spectra, we identified the dr as > 20:1. [c]Yield of isolated product. [d](R)-(-)-1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate. [e]**2a** (4 equiv), and $ZnMe_2$ (4 equiv). [f]**2a** (5 equiv), and $ZnMe_2$ (4 equiv).

On the basis of this initial observation, we used 5-methoxysalicylaldehyde (**1a**), 3-methoxyprop-1-yne (**2a**), and 6,6-dimethyl-1-vinylcyclohex-1-ene (**3a**) as model substrates for further optimization (Table 1). Various acids were initially evaluated in toluene at 40 °C (entries 1-9). The experimental results indicated that HCO_2H is a beneficial acid. By using the ideal acid, we discovered that the stoichiometric ratio of **2a** and $ZnMe_2$ in alkynylation sequence effectively facilitated the desired transformation (entries 9-11). We then screened several organic solvents, including THF, hexane and CH_2Cl_2 (entries 12-15). As a result, CH_2Cl_2 was found to be the best choice at room temperature, and the anticipated spirocycle containing product **4a** can be produced in 46% yield. We also performed a stepwise investigation under the optimal conditions but leading to a lower yield (22%, for details see ESI). So we proposed that the existence of $ZnMe_2$ may play a very significant role in the one-pot process.

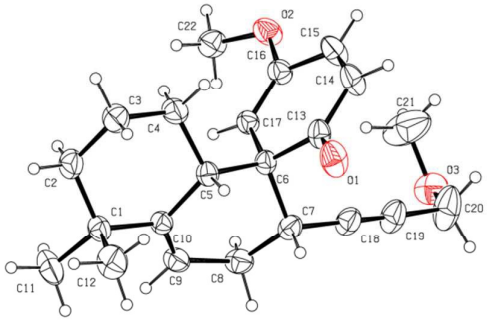


Figure 2. The X-ray structure of **4a**.

Having identified optimal reaction conditions (Table 1, entry 15), we first examined the substrate scope of this transformation with respect to the substituted salicylaldehydes partner. Table 2 shows that the electronic effect of the substrates is very significant. Electron-donating groups, such as dimethoxy (**4g**), methoxy (**4a,h**), and methyl (**4b**) are more favorable for the envisioned spirocycle products than the electron-withdrawing groups, such as bromo (**4d**), chloro (**4e**), and ester (**4f**). The reaction is also restricted to the terminal alkyne (**4a, 4h-k**). The steric effect of these electron-rich alkynes exerts a great impact on the yields(23%-46%). Functionalized 1,3-butadienes were also investigated. We obtained both spirocycle products (**4l-1, 4m-1, 4n-1**) and benzopyran compounds (**4l-2, 4m-2, 4n-2**) when the reaction

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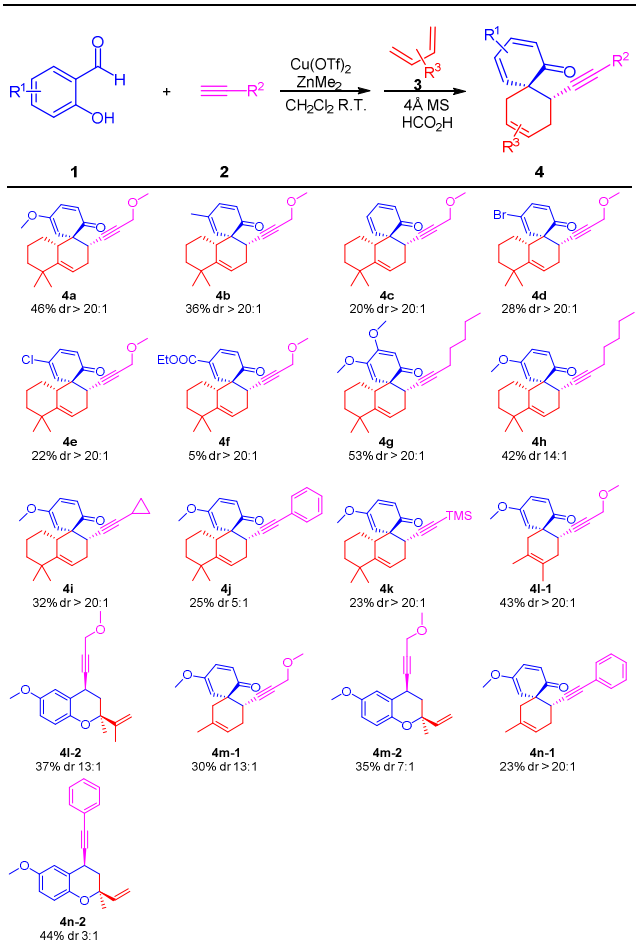
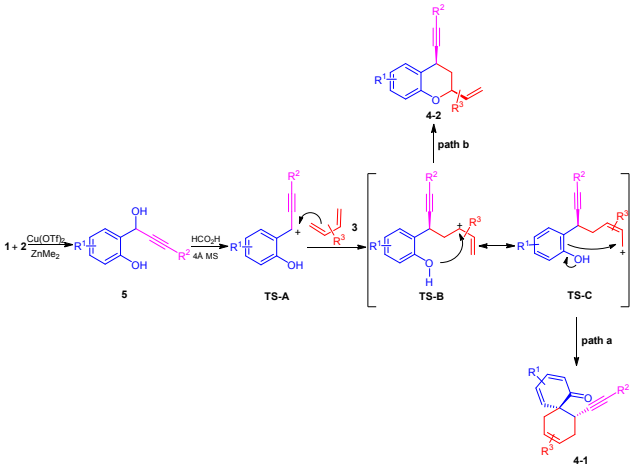
was treated with isoprene or 2,3-dimethyl-1,3-butadiene. Benzopyran compounds were not observed when using 6,6-dimethyl-1-vinylcyclohex-1-ene (**3a**) as diene (Table 2, **4a-k**). We then speculated that the benzopyran products corresponding to **3a** are unstable under acidic conditions.

Table 2 Substrate scope of alkynylation/dearomatizative cyclization toward spirocycle compounds[a]



[a]For all compounds, dr was determined by ^{1}H NMR spectroscopy, if diastereoisomers could not be detected in ^{1}H NMR spectra, we identified the dr as > 20:1. **4g** and **4i** were also analysed by HPLC (see ESI).

Based on these results and our previous findings, a plausible reaction mechanism for this spirocyclization is illustrated in Scheme 2. The reaction of $ZnMe_2$ with terminal alkyne (**2**) generated an active alkynylzinc,[20] which attacked the substituted salicylaldehyde (**1**) to form alcohol (**5**). Under acidic conditions, **5** was converted into carbocation **TS-A**, which was difunctionally stabilized by a phenyl group and an acetylenyl group through conjugation effects. The formed carbocation **TS-A** underwent electrophilic addition with diene **3** to deliver the resonance hybrids TS-B and TS-C. TS-C followed by enol-keto tautomerization of the phenol ring to produce spirocycle **4-1** (path a). At the same time, **TS-B** underwent intramolecular nucleophilic addition to form the benzopyran compound **4-2** through path b.



Scheme 2. Plausible reaction mechanism.

Conclusions

We developed an approach to construct spiro[5.5]undecanes. The $ZnMe_2$-promoted alkynylation of salicylaldehyde and HCO_2H-mediated dearomatizative cyclization occurred in sequence in a one-pot process, which not only involves readily available starting materials but also demonstrates high diastereoselectivities. Utilizing multicomponent synthesis and one-pot process as the core strategies, a number of spirocycles were prepared smoothly.

Notes and references

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1 Reviews on spirocycle compounds: A special issue “Spiro Compounds”, ed. G. L. Plourde, *Molecules*, 2008, **13**.
2 (a) J. J. Sims, G. H. Y. Lin, R. M. Wing, *Tetrahedron Lett.,* 1974, **15**, 3487; (b) D. J. Kennedy, I. A. Selby, R. H. Thomson, *Phytochemistry*, 1988, **27**, 1761; (c) Y. Asakawa, T. Motoo, T. Masuya, J.-P. Frahm, *Phytochemistry,* 1990, **29**, 1577; (d) E. C. d. C. Araújo, M. A. S. Lima, E. R. Silveira, *Magn. Reson. Chem.,* 2004, **42**, 1049; (e) K. M. Brundret, W. Dalziel, B. Hesp, J. A. J. Jarvis, S. Neidle, *J. Chem. Soc., Chem. Commun.,* 1972, 1027.
3 (a) C. S. Vairappan, M. Daitoh, M. Suzuki, T. Abe, M. Masuda, *Phytochemistry,* 2001, **58**, 291; (b) C. S. Vairappan, *Biomol. Eng.,* 2003, **20**, 255; (c) HeLa: IC50 = 4.1 mM (lag phase), 1.3 mM (log phase); Hep-2: IC50 = 2.4 mM (lag phase), 2.0 mM (log phase); T. Dias, I. Brito, L. Moujir, N. Paiz, J. Darias, M. Cueto, *J. Nat. Prod.,* 2005, **68**, 1677.
4 (a) R. A. Buchnall, H. Moores, R. Simms, B. Hesp, *Antimicrob.Agents Chemother.*, 1973, **4**, 294; (b) S. Ikegami, T. Taguchi, M. Ohashi, M. Oguro, Y. Mano, *Nature,* 1978, **275**, 458.
5 (a) L. Pouységu, S. Chassaing, D. Dejugnac, A.-M. Lamidey, K. Miqueu, J.-M. Sotiropoulos, S. Quideau, *Angew. Chem. Int. Ed.*, 2008, **47**, 3552; (b) T. Dohi, A. Maruyama, N. Takenaga, K. Senami, Y. Minamitsuji, H. Fujioka, S. B. Caemmerer, and Y. Kita, *Angew. Chem. Int. Ed.*, 2008, **47**, 3787; (c) T. Dohi, N.

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DOI: 10.1039/C6RA02463G

Takenaga, T. Nakae, Y. Toyoda, M. Yamasaki, M. Shiro, H. Fujioka, A. Maruyama, and Y. Kita, *J. Am. Chem. Soc.,* 2013, **135**, 4558; (d) M. Uyanik, T. Yasui, and K. Ishihara, *Angew. Chem. Int. Ed.,* 2010, **49**, 2175; (e) M. Uyanik, T. Yasui, and K. Ishihara, *Angew. Chem. Int. Ed.,* 2013, **52**, 9215; (f) M. Uyanik, N. Sasakura, E. Kaneko, K. Ohori, and K. Ishihara, *Chem. Lett.,* 2015, **44**, 179; (g) M. Uyanik, N. Sasakura, M. Kuwahata, Y. Ejima, and K. Ishihara, *Chem. Lett.,* 2015, **44**, 381.

6 (a) J. X. Liang, J. B. Chen, F. X. Du, X. H. Zeng, L. Li, and H. B. Zhang, *Org. Lett.,* 2009, **11**, 2820; (b) H. Liang, and M. A. Ciufolini, *Chem. Eur. J.,* 2010, **16**, 13262; (c) C. Zheng, L. Wang, J. J. Li, L. F. Wang, and D. Z. G. Wang, *Org. Lett.,* 2013, **15**, 4046; (d) A. M. Harned, *Tetrahedron Lett.,* 2014, **55**, 4681; (e) H. Abdellaoui, J. X. Xu, *Tetrahedron,* 2014, **70**, 4323; (f) D.-Y. Zhang, L. Xu, H. Wu, and L.-Z. Gong, *Chem. Eur. J.,* 2015, **21**, 10314; (g) J.-C. Andrez, M.-A. Giroux, J. Lucien, and S. Canesi, *Org. Lett.,* 2010, **12**, 4368.

7 (a) T. Nemoto, Y. Ishige, M. Yoshida, Y. Kohno, M. Kanematsu, and Y. Hamada, *Org. Lett.,* 2010, **12**, 5020; (b) Q.-F. Wu, W.-B. Liu, C.-X. Zhuo, Z.-Q. Rong, K.-Y. Ye, and S.-L. You, *Angew. Chem. Int. Ed.,* 2011, **50**, 4455; (c) S. Rousseaux, J. G. Fortanet, M. A. D. A. Sanchez, and S. L. Buchwald, *J. Am. Chem. Soc.,* 2011, **133**, 9282.

8 A. Rudolph, P. H. Bos, A. Meetsma, A. J. Minnaard, and B. L. Feringa, *Angew. Chem. Int. Ed.,* 2011, **50**, 5834.

9 T. Oguma, and T. Katsuki, *Chem. Commun.,* 2014, **50**, 5053.

10 (a) J. Nan, Z. J. Zuo, L. Luo, L. Bai, H. Y. Zheng, Y. N. Yuan, J. J. Liu, X. J. Luan, and Y. Y. Wang, *J. Am. Chem. Soc.,* 2013, **135**, 17306; (b) Z. J. Zuo, X. Yang, J. J. Liu, J. Nan, L. Bai, Y. Y. Wang, and Xinjun Luan, *J. Org. Chem.,* 2015, **80**, 3349; (c) J. Zheng, S.-B. Wang, C. Zheng, and S.-L. You, *J. Am. Chem. Soc.,* 2015, **137**, 4880.

11 (a) A. Seoane, N. Casanova, N. Quiñones, J. L. Mascareñas, and M. Gulías, *J. Am. Chem. Soc.,* 2014, **136**, 7607; (b) S. Kujawa, D. Best, D. J. Burns, and H. W. Lam, *Chem. Eur. J.,* 2014, **20**, 8599.

12 S. L. Gu, L. Luo, J. J. Liu, L. Bai, H. Y. Zheng, Y. Y. Wang, and X. J. Luan, *Org. Lett.,* 2014, **16**, 6132.

13 H. Y. Zheng, L. Bai, J. J. Liu, J. Nan, Z. J. Zuo, L. Yang, Y. Y. Wang and X. J. Luan, *Chem. Commun.,* 2015, **51**, 3061.

14 B. S. Matsuura, A. G. Condie, R. C. Buff, G. J. Karahalis, and C. R. J. Stephenson, *Org. Lett.,* 2011, **13**, 6320.

15 J. C. Green and T. R. R. Pettus, *J. Am. Chem. Soc.,* 2011, **133**, 1603.

16 E. E. Podlesny, P. J. Carroll, and M. C. Kozlowski, *Org. Lett.,* 2012, **14**, 4862.

17 Y. S. Rozhkova, K. A. Galata, A. A. Gorbunov, Y. V. Shklyaev, M. A. Ezhikova, and M. I. Kodess, *Synlett,* 2014, **25**, 2617.

18 G. F. Han, Y. X. Liu, and Q. M. Wang, *Org. Lett.,* 2014, **16**, 3188.

19 J. D. Shao, L. Q. Li, J. Zhang, T. Tian, J. J. Xue, Y. Zhang, and Y. Li, *Synlett,* 2015, **26**, 827.

20 L. Pu, and H.-B. Yu, *Chem. Rev.,* 2001, **101**, 757.

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Graphical abstract

One-pot process to construct spiro[5.5]undecanes.