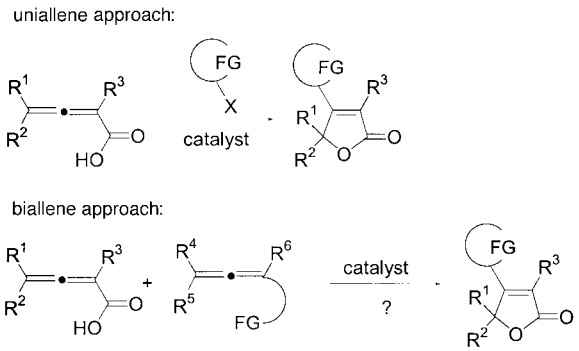
[1] E. G. Janzen, D. E. Nutter, Jr., E. R. Davis, B. J. Blackburn, J. L. Poyer, P. B. McCay, *Can. J. Chem.* **1978**, *56*, 2237.
[2] a) R. A. Floyd, K. Hensley, *Ann. N.Y. Acad. Sci.* **2000**, *899*, 222; b) R. A. Floyd, *Adv. Pharmacol.* **1997**, *38*, 361.
[3] H. Miyabe, M. Ueda, T. Naito, *J. Org. Chem.* **2000**, *65*, 5043.
[4] A. Jeevanandam, C. Cartwright, Y. C. Ling, *Synth. Commun.* **2000**, *30*, 3153.
[5] G. K. Friestad, *Tetrahedron* **2001**, *57*, 5461.
[6] a) E. J. Corey, S. G. Pyne, *Tetrahedron Lett.* **1983**, *24*, 2821; b) T. Kiguchi, K. Tajiri, I. Ninomiya, T. Naito, H. Hiramatsu, *Tetrahedron Lett.* **1995**, *36*, 253; c) T. Naito, K. Nakagawa, T. Nakamura, A. Kasei, I. Ninomiya, T. Kiguchi, *J. Org. Chem.* **1999**, *64*, 2003; d) J. Tormo, D. S. Hays, G. C. Fu, *J. Org. Chem.* **1998**, *63*, 201; e) J. Marco-Contelles, P. Gallego, M. Rodriguez-Fernandez, N. Khiar, C. Destabel, M. Bernabe, A. Martinez-Grau, J. L. Chiara, *J. Org. Chem.* **1997**, *62*, 7397; f) H. Miyabe, S. Kanehira, K. Kume, H. Kandori, T. Naito, *Tetrahedron* **1998**, *54*, 5883; g) H. Miyabe, M. Torieda, K. Inoue, K. Tajiri, T. Kiguchi, T. Naito, *J. Org. Chem.* **1998**, *63*, 4397; h) A. Boiron, P. Zillig, D. Faber, B. Giese, *J. Org. Chem.* **1998**, *63*, 5877; i) I. Storch de Gracia, H. Dietrich, S. Bobo, J. L. Chiara, *J. Org. Chem.* **1998**, *63*, 5883; j) I. S. de Gracia, S. Bobo, M. D. Martin Ortega, J. L. Chiara, *Org. Lett.* **1999**, *1*, 1705; k) K. C. Nicolaou, X. Huang, N. Giuseppone, P. B. Rao, M. Bella, M. V. Reddy, S. A. Snyder, *Angew. Chem.* **2001**, *113*, 4841 – 4845; *Angew. Chem. Int. Ed.* **2001**, *40*, 4705.
[7] a) C. F. Sturino, A. G. Fallis, *J. Am. Chem. Soc.* **1994**, *116*, 7447; b) C. F. Sturino, A. G. Fallis, *J. Org. Chem.* **1994**, *59*, 6514; c) P. Tauh, A. G. Fallis, *J. Org. Chem.* **1999**, *64*, 6960; d) D. Riber, R. Hazell, T. Skrydstrup, *J. Org. Chem.* **2000**, *65*, 5382.
[8] N. Taniguchi, T. Hata, M. Uemura, *Angew. Chem.* **1999**, *111*, 1311; *Angew. Chem. Int. Ed.* **1999**, *38*, 1232.
[9] E. J. Roskamp, S. F. Pedersen, *J. Am. Chem. Soc.* **1987**, *109*, 6551.
[10] a) T. Shono, N. Kise, T. Fujimoto, *Tetrahedron Lett.* **1991**, *32*, 525; b) T. Shono, N. Kise, N. Kunimi, R. Nomura, *Chem. Lett.* **1991**, 2191; c) T. Shono, N. Kise, T. Fujimoto, A. Yamanami, R. Nomura, *J. Org. Chem.* **1994**, *59*, 1730.
[11] T. Imamoto, S. Nishimura, *Chem. Lett.* **1990**, 1141.
[12] E. J. Enholm, D. C. Forbes, D. P. Holub, *Synth. Commun.* **1990**, *20*, 981.
[13] T. Hanamoto, J. Inanaga, *Tetrahedron Lett.* **1991**, *32*, 3555.
[14] F. Machrouhi, J.-L. Namy, *Tetrahedron Lett.* **1999**, *40*, 1315.
[15] N. Taniguchi, M. Uemura, *J. Am. Chem. Soc.* **2000**, *122*, 8301.
[16] Nitrones were prepared according to literature procedures: a) A. Dondoni, S. Franco, F. Junquera, P. Merino, T. Tejero, *Synth. Commun.* **1994**, *24*, 2537; S. Franco, F. L. Merchan, P. Merino, T. Tejero, *Synth. Commun.* **1995**, *25*, 2275.
[17] A. S. Kende, J. S. Mendoza, *Tetrahedron Lett.* **1991**, *32*, 1699.
[18] As indicated by the formation of the cyclic carbamate **5** on treating the amino alcohol **3** with phosgene in pyridine, and by comparison of **3** with a sample of the isomeric *trans* amino alcohol.

Oxidative Cyclization – Dimerization Reaction of 2,3-Allenoic Acids and 1,2-Allenyl Ketones: An Efficient Synthesis of 4-(3′-Furanyl)butenolide Derivatives**

Shengming Ma* and Zhanqian Yu

Allenes are a class of compounds with interesting reactivities owing to the presence of two cumulative carbon-carbon double bonds.[1] As a result of the axial chirality as well as the substituent-loading capability, allenes show great potential in organic synthesis in terms of chirality transfer[2] and diversity. Recently, we[3–5] and others[6–14] established the cycloisomerization of functionalized allenes and the coupling – cyclization of functionalized allenes with organic halides for the synthesis of carbo- and heterocyclic compounds based on transition-metal-catalyzed or mediated cyclization of functionalized allenes.[14] However, to the best of our knowledge, no protocol has been established in the area of cyclization – dimerization reactions between two different classes of functionalized allenes to give interesting cyclic compounds in a single step (Scheme 1). The formidable *challenge* is to match the reactivities of two different classes of allenes.



Scheme 1. Cyclization – dimerization reactions of functionalized allenes to give butenolide derivatives.

With this idea in mind, we screened different combinations of several functionalized allenes, for example, 2,3-allenoic acids,[3] 2,3-allenols,[4a,b] 2,3-allenamides,[4c] and 1,2-allenyl ketones.[5] Fortunately, after numerous trial and error reactions, we observed the $[PdCl_2(MeCN)_2]$-catalyzed (5 mol %)

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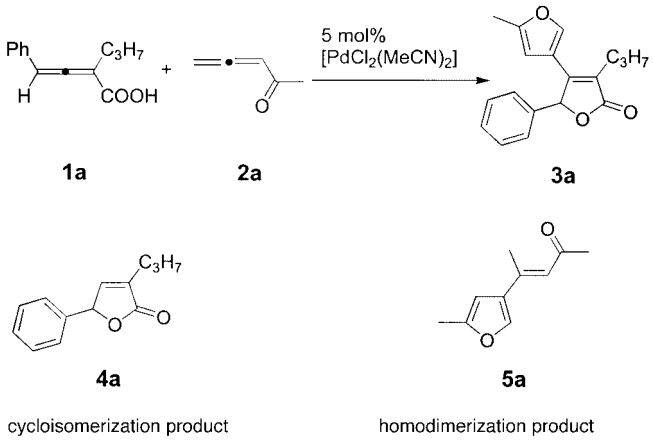
cyclization – dimerization reaction of allenoic acid **1a** with ketone **2a** in THF, which afforded furanone **3a** in 14% yield (Scheme 2; Table 1, entry 2). The reaction can also be carried out in methanol, CH_2Cl_2, acetone, toluene, DMA (N,N-dimethylacetamide), and acetonitrile. In CH_2Cl_2 or toluene, the major by-product is the cycloisomerization[3d, 7] product of **1a**, that is, furanone **4a** (Scheme 2; Table 1, entries 1 and 6). The reaction in DMA afforded **3a** exclusively in 76% yield (Table 1, entry 4). The best results were obtained in MeCN (Table 1, entry 11) with 5 equivalents of **2a**. Hashmi and co-workers established the Pd^{II}- and Au^{III}-catalyzed cyclization – homodimerization reaction of 1,2-allenyl ketones which led to 3-(3′-oxo-1′-alkenyl)furans and 2-(3′-oxo-1′-alkenyl)- or 2-(3′-oxo-1′-alkanyl)furans, respectively.[15, 16] In this case, **5a** (the homodimerization product of **2a**) was formed in 13% yield (based on the initial amount of **2a** used (Scheme 2)). With smaller amounts of **2a**, the reaction in acetonitrile also afforded **4a** as the by-product (Table 1, entries 7 – 10).



Scheme 2. Cyclization – dimerization reaction of allenoic acid **1a** with ketone **2a**

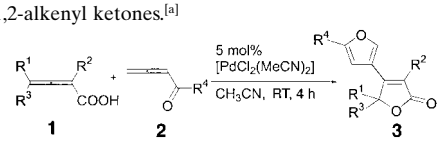
Table 1. Cyclization – dimerization reaction of **1a** and **2a**.[a]

Entry	**2a** [equiv]	Solvent	Time [h]	Yield (**3a**) [%]	Yield (**4a**) [%]
1	5	CH_2Cl_2	11	23	14
2	5	THF	11	14	0
3	5	acetone	11	40	0
4	5	DMA	17.5	76	0
5	5	methanol	12	30	trace
6	5	toluene	16.5	13	18
7	1	CH_3CN	10	27	30
8	2	CH_3CN	22	42	30
9	3	CH_3CN	11.5	57	12
10	4	CH_3CN	11	69	6
11	5	CH_3CN	4	90	0

[a] The reaction of **1a** (0.25 mmol), **2a** (1.25 mmol), and $[PdCl_2(MeCN)_2]$ (5 mol%) was carried out in the solvent (3 mL).

Some typical results are summarized in Table 2: 1) these are the first examples of sequential cyclization – dimerization reactions of two different functionalized allenes; 2) various substituents are tolerated and mono-, di-, and trisubstituted 2,3-allenoic acids can be used; 3) the reaction can occur under mild conditions (room temperature, 4 h) and the yields range from moderate to fairly good.

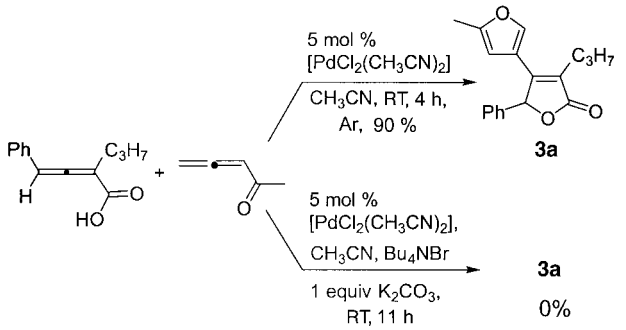
Table 2. Pd^{II}-catalyzed cyclization – dimerization reaction of 2,3-allenoic acids and 1,2-alkenyl ketones.[a]



Entry	**1** R^1	**1** R^2	**1** R^3	**2** R^4	Yield (**3**) [%]
1	Ph	n-C_3H_7	H (**1a**)	CH_3 (**2a**)	90 (**3a**)
2	Ph	$PhCH_2$	H (**1b**)	CH_3 (**2a**)	92 (**3b**)
3	Ph	CH_3	Et (**1c**)	CH_3 (**2a**)	85 (**3c**)
4	Ph	Allyl	H (**1d**)	CH_3 (**2a**)	61 (**3d**)
5	α-naphthyl	n-C_3H_7	H (**1e**)	CH_3 (**2a**)	86 (**3e**)
6	CH_3	$PhCH_2$	H (**1f**)	CH_3 (**2a**)	90 (**3f**)
7	n-C_7H_{15}	H	H (**1g**)	CH_3 (**2a**)	69 (**3g**)
8	Ph	n-C_3H_7	H (**1a**)	n-C_4H_9 (**2b**)	84 (**3h**)
9	Ph	CH_3	Et (**1c**)	n-C_4H_9 (**2b**)	86 (**3i**)
10	n-C_7H_{15}	H	H (**1g**)	n-C_4H_9 (**2b**)	69 (**3j**)
11	Ph	n-C_3H_7	H (**1a**)	$PhCH_2$ (**2c**)	74 (**3k**)
12	Ph	CH_3	Et (**1c**)	$PhCH_2$ (**2c**)	84 (**3l**)
13	n-C_7H_{15}	H	H (**1g**)	$PhCH_2$ (**2c**)	71 (**3m**)

[a] The reaction of **1** (0.25 mmol), **2** (1.25 mmol), and $[PdCl_2(MeCN)_2]$ (5 mol%) was carried out in CH_3CN (3 mL).

To clarify the mechanism of this reaction, two control experiments were conducted (Scheme 3): Under an argon atmosphere, the reaction occurs smoothly to afford **3a** in 90% yield, which indicates that air does not participate in the catalytic cycle. However, the reaction does not yield **3a** in the presence of K_2CO_3 (1 equiv), which indicates that HCl may be formed by the loss of two protons from both starting materials and play an important role in this reaction.



Scheme 3. The reaction does not occur in the presence of K_2CO_3 (1 equiv), which indicates that HCl may be formed by the loss of two protons from both starting materials.

A further study shows that the reaction also affords 4,5-dimethyleneocta-2,7-dione (**6a**) and its C=C double-bond isomers **7a** and **8a** as by-products (Scheme 4). Based on these facts, a plausible mechanism was proposed for this reaction: the Pd^0 species generated after the reductive elimination of **9a** reacts with penta-3,4-dienone (2 equiv) to form the cyclic Pd intermediate **10a**, which can be protonated with the HCl (2 equiv, generated in situ) to form **6a**, **7a**, and **8a**. The $[PdL_nCl_2]$ is regenerated and can reenter the catalytic cycle (Scheme 5).[17]

In conclusion, an oxidative cyclization – dimerization reaction between two different allenes provides an efficient route to polysubstituted 4-(3′-furanyl)-2(5*H*)-furanones **3**, which

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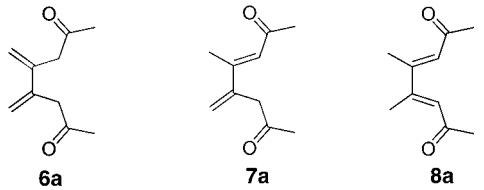
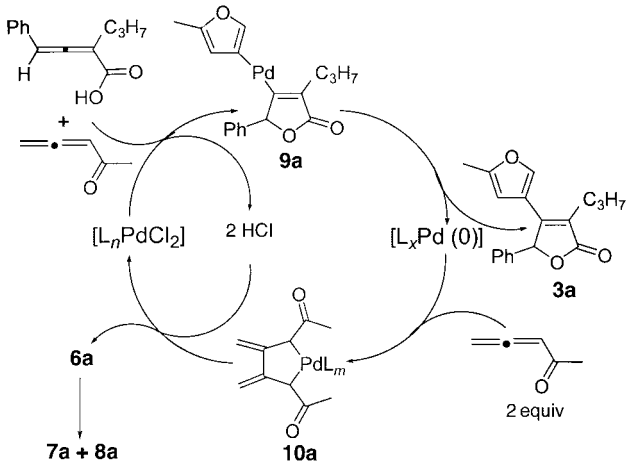


[a] Yields are calculated based on penta-3,4-dienone used.

Scheme 4. 4,5-Dimethyleneocta-2,7-dione (**6a**) and its C=C double-bond isomers **7a** and **8a** are by-products in the reaction of **1a** and **2a**. [a] Yields are calculated based on **2a**.



Scheme 5. Proposed catalytic cycle for the cyclization–dimerization reaction.

are not readily available. Further studies into the scope, mechanism, and synthetic applications of this reaction are being carried out in our laboratory.

Experimental Section

Typical procedure: $[PdCl_2(MeCN)_2]$ (3 mg, 5 mol%) was added to a mixture of **1a** (50 mg, 0.248 mmol) and **2a** (103 mg, 1.26 mmol) in CH_3CN (3 mL), and the mixture was stirred at room temperature for 4 h. Evaporation and chromatography on silica gel (petroleum ether/diethyl ether 3:1) afforded pure **3a** (63 mg, 90%) as a white solid. M.p. 84–85 °C (ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.41-7.21$ (m, 5H), 7.18 (s, 1H), 6.04 (s, 1H), 5.89 (s, 1H), 2.62-2.50 (m, 2H), 2.24 (s, 3H), 1.78–1.63 (m, 2H), 1.06 ppm (t, $J = 7.33$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): $\delta = 13.30$, 14.14, 21.39, 26.51, 82.99, 104.77, 118.09, 126.24, 127.86, 129.04, 129.55, 135.85, 141.42, 150.37, 153.82, 174.30 ppm; MS (70 eV): *m/z* (%): 283 (28.39) [M^++1], 282 (100) [M^+]; IR (neat): $\tilde{\nu} = 2960$, 2920, 2869, 1732, 1654, 1603 cm^{-1}; elemental analysis: calcd for $C_{18}H_{18}O_3$ (%): C 76.57, H 6.43; found C 76.46, H 6.45.

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[1] a) H. F. Schuster, G. M. Coppola, *Allenes in Organic Synthesis*, Wiley, New York, **1984**; b) S. Patai, *The Chemistry of Ketenes, Allenes, and Related Compounds, Part 1*, Wiley, New York, **1980**.

[2] For some typical examples of axial chirality transfer, see: a) G. Kresze, L. Kloimstein, W. Runge, *Justus Liebigs Ann. Chem.* **1976**, *64*, 979; b) S. Musierowicz, A. E. Wroblewski, *Tetrahedron* **1978**, *34*, 461; c) J. A. Marshall, M. A. Wolf, E. M. Wallace, *J. Org. Chem.* **1997**, *62*, 367; d) S. Ma, S. Wu, *Chem. Commun.* **2001**, 441.

[3] For the synthesis of butenolides from 2,3-allenoic acids, see: a) S. Ma, Z. Shi, *J. Org. Chem.* **1998**, *63*, 6387; b) S. Ma, Z. Shi, S. Wu, *Tetrahedron: Asymmetry* **2001**, *12*, 193; c) S. Ma, S. Wu, *J. Org. Chem.* **1999**, *64*, 9314; d) S. Ma, Z. Yu, S. Wu, *Tetrahedron* **2001**, *57*, 1585.

[4] a) For the stereoselective synthesis of epoxides, see: S. Ma, S. Zhao, *J. Am. Chem. Soc.* **1999**, *121*, 7943; b) For the synthesis of 2,5-dihydrofurans, see: S. Ma, W. Gao, *Tetrahedron Lett.* **2000**, *41*, 8933; c) for the synthesis of 4-halopyrrol-2(5*H*)-ones, see: S. Ma, H. Xie, *Org. Lett.* **2000**, *2*, 3801; d) for the synthesis of carbocycles, see: S. Ma, S. Zhao, *Org. Lett.* **2000**, *2*, 2495.

[5] For the synthesis of polysubstituted furans from 1,2-allenyl ketones, see: a) S. Ma, Z. Zhang, *Chem. Commun.* **2000**, 117; b) S. Ma, L. Li, *Org. Lett.* **2000**, *2*, 941.

[6] For catalytic cycloisomerization of allenols, see: a) J. A. Marshall, X. Wang, *J. Org. Chem.* **1990**, *55*, 2995; b) J. A. Marshall, X. Wang, *J. Org. Chem.* **1991**, *56*, 960; c) L. I. Olsson, A. Claesson, *Synthesis* **1979**, 743; d) S. S. Nikam, K. H. Chu, K. K. Wang, *J. Org. Chem.* **1986**, *51*, 745; e) R. Gelin, S. Gelin, M. Albrand, *Bull. Soc. Chim. Fr.* **1972**, 1946; f) J. A. Marshall, C. A. Sehon, *J. Org. Chem.* **1995**, *60*, 5966; g) J. A. Marshall, R. H. Yu, J. F. Perkins, *J. Org. Chem.* **1995**, *60*, 5550; h) A. Hoffmann-Roder, N. Krause, *Org. Lett.* **2001**, *3*, 2537.

[7] For catalytic cycloisomerization of 2,3-allenoic acids, see: J. A. Marshall, G. S. Bartley, E. M. Wallace, *J. Org. Chem.* **1996**, *61*, 5729.

[8] For the Pd^0-catalyzed coupling–cyclization reaction of allenols with aryl or vinyl halides, see: a) K. Uemura, D. Shiraishi, M. Noziri, Y. Inoue, *Bull. Chem. Soc. Jpn.* **1999**, 1063; b) S.-K. Kang, T.-G. Baik, A. N. Kulak, *Synlett* **1999**, 324; c) S.-K. Kang, T. Yamaguchi, S.-J. Pyun, Y.-T. Lee, T.-G. Baik, *Tetrahedron Lett.* **1998**, *39*, 2127; d) R. D. Walkup, L. Guan, Y. S. Kim, S. W. Kim, *Tetrahedron Lett.* **1995**, *36*, 3805; e) R. D. Walkup, L. Guan, M. D. Mosher, S. W. Kim, Y. S. Kim, *Synlett* **1993**, 88.

[9] a) For the Ru-catalyzed reaction of allenols in the presence of CO, see: E. Yoneda, T. Kaneko, S.-W. Zhang, K. Onitsuka, S. Takahashi, *Org. Lett.* **2000**, *2*, 441; b) for the Ru-catalyzed cyclization of allenols with α,β-unsaturated enones, see: B. M. Trost, A. B. Prinkerton, *J. Am. Chem. Soc.* **1999**, *121*, 10842.

[10] For the Pd^0-catalyzed coupling–cyclization reaction of allenic amides with aryl or vinyl halides, see: a) H. Ohno, M. Anzai, A. Toda, S. Ohishi, N. Fujii, T. Tanaka, Y. Takemoto, T. Ibuka, *J. Org. Chem.* **2001**, *66*, 4904; b) S.-K. Kang, K.-J. Kim, *Org. Lett.* **2001**, *3*, 511; c) M. Anzai, A. Toda, H. Ohno, Y. Takemoto, N. Fujii, T. Ibuka, *Tetrahedron Lett.* **1999**, *40*, 7393; d) F. P. J. T. Rutjes, K. C. M. F. Tjen, L. B. Wolf, W. F. J. Karstens, H. E. Schoemaker, H. Hiemstra, *Org. Lett.* **1999**, *1*, 717; e) H. Ohno, A. Toda, Y. Miwa, T. Taga, E. Osawa, Y. Yamaoka, N. Fuji, T. Ibuka, *J. Org. Chem.* **1999**, *64*, 2992; f) W. F. J. Karstens, M. Stol, F. P. J. T. Rutjes, H. Hiemstra, *Synlett* **1998**, 1126; g) W. F. J. Karstens, F. P. J. T. Rutjes, H. Hiemstra, *Tetrahedron Lett.* **1997**, 6275; h) I. W. Davies, D. I. C. Scopes, T. Gallagher, *Synlett* **1993**, 85.

[11] For the Pd-catalyzed coupling–cyclization reaction of allenic amides with allylic halides, see: a) W. F. J. Karstens, D. Klomp, F. P. J. T. Rutjes, H. Hiemstra, *Tetrahedron* **2001**, *57*, 5123; b) M. Kimura, S. Tanaka, Y. Tamaru, *J. Org. Chem.* **1995**, *60*, 3764; c) M. Kimura, K. Fugami, S. Tanaka, Y. Tamaru, *J. Org. Chem.* **1992**, *57*, 6377; d) J. S. Prasad, L. S. Liebeskind, *Tetrahedron Lett.* **1988**, *29*, 4257.

[12] For Ag^+-catalyzed cycloisomerization of amino allenes, see: a) M. O. Amombo, A. Hausherr, H.-U. Reissig, *Synlett* **1999**, 1871; b) I. W. Davies, T. Gallagher, R. B. Lamont, D. I. C. Scopes, *J. Chem. Soc. Chem. Commun.* **1992**, 335; c) D. N. A. Fox, D. Lathbury, M. F. Mahon, K. C. Molloy, T. Gallagher, *J. Chem. Soc. Chem. Commun.* **1989**, 1073; d) J. S. Prasad, L. S. Liebeskind, *Tetrahedron Lett.* **1988**, *29*, 4253; e) R. Kinsman, D. Lathbury, P. Vernon, T. Gallagher, *J. Chem. Soc. Chem. Commun.* **1987**, 243.

[13] a) For Pd-catalyzed cycloisomerization of 2-(allenyl)malonates, see: S. Kamijo, Y. Yamamoto, *Tetrahedron Lett.* **1999**, *40*, 1747; M. Meguro, Y. Yamamoto, *J. Org. Chem.* **1999**, *64*, 694; M. Meguro, S. Kamijo, Y. Yamamoto, *Tetrahedron Lett.* **1996**, *37*, 7453; b) for Pd-catalyzed coupling–cyclization of 2-(allenyl)malonates with organic halides, see: L. Besson, J. Bazin, J. Gore, B. Cazes, *Tetrahedron Lett.* **1994**, *35*, 2881; M. Ahmar, B. Cazes, J. Gore, *Tetrahedron Lett.* **1985**, *26*, 3795.

[14] For a review on the palladium-catalyzed chemistry of allenes, see: R. Zimmer, C. U. Dinesh, E. Nandanan, F. A. Khan, *Chem. Rev.* **2000**, *100*, 3067.

[15] For dimerization of 1,2-allenyl ketones, see: a) A. S. K. Hashmi, J. -H. Choi, J. W. Bats, *J. Prakt. Chem.* **1999**, *341*, 342; b) A. S. K. Hashmi, T. L. Ruppert, T. Knöfel, J. W. Bats, *J. Org. Chem.* **1997**, *62*, 7295; c) A. S. K. Hashmi, *Angew. Chem.* **1995**, *105*, 1749; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1581; d) A. S. K. Hashmi, L. Schwarz, J.-H. Choi, T. M. Frost, *Angew. Chem.* **2000**, *112*, 2382; *Angew. Chem. Int. Ed.* **2000**, *39*, 2285.

[16] For a recent highlight, see: A. S. K. Hashmi, *Angew. Chem.* **2000**, *112*, 3737; *Angew. Chem. Int. Ed.* **2000**, *39*, 3590.

[17] For protonolysis of Pd enolate to regenerate divalent palladium, see: Z. Wang, X. Lu, *J. Org. Chem.* **1996**, *61*, 2254.

Enantiospecific Synthesis of the Bridged Pyrrolizidine Core of Asparagamine A: Dipolar Cycloadditions of Azomethine Ylides Derived from the Sulfonylation of Vinylogous Amides.**

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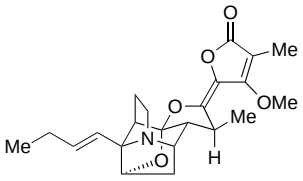
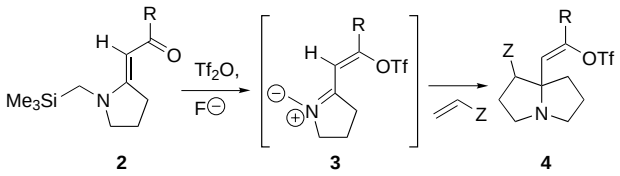
The efficient construction of highly functionalized pyrrolizidines is regarded as an important synthetic challenge owing to the diverse array of complex alkaloids that possess the necine skeleton. Asparagamine A (**1**) is a bridged pyrrolizidine alkaloid isolated from *Asparagus racemosus* that incorporates an intricate and rigid pentacyclic core[1] akin to the insecticidal stemofoline alkaloids,[2] natural products that have garnered considerable synthetic interest.[3] In vivo biological assays of **1** revealed potent antioxytocin activity,[4] despite its lack of structural homology with known oxytocin receptor antagonists.[5] We report herein an enantiospecific synthesis of the bridged pyrrolizidine skeleton of **1** that utilizes a complex intramolecular 1,3-dipolar cycloaddition as the key transformation.[6]



1

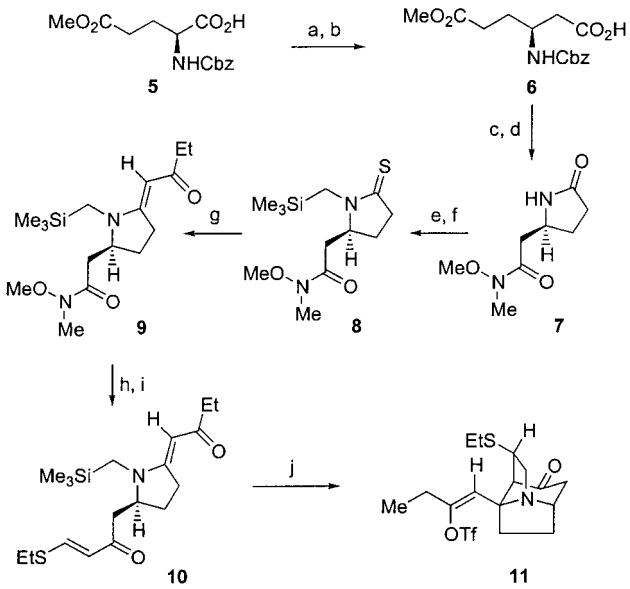
In the context of the synthesis of five-membered N heterocycles, azomethine ylides have proven to be valuable intermediates in a variety of 1,3-dipolar cycloadditions. A plethora of methods for the generation of these reactive intermediates exists and includes deprotonation, desilylation, or destannylation of imine or iminium salts, as well as the thermolysis or photolysis of aziridines.[7] However, in surveying the known procedures and substrates in the context of constructing the pyrrolizidine cage of **1**, a key challenge in this synthetic approach involves the direct installation of the angular C8 *E*-1-butenyl substituent during the cycloaddition reaction. As a result, vinylogous amides such as **2** (Scheme 1) were examined as potential precursors to azomethine ylides such as **3** through sequential O-sulfonylation[8] and desilylation.[9, 10] A 1,3-dipolar cycloaddition of **3** with a suitable dipolarophile would presumably lead to a pyrrolizidine that incorporates an enol triflate moiety at the angular position of **4**, a structure that maps directly onto the framework of **1**.



2 **3** **4**

Scheme 1. Vinylogous amides (e.g. **2**) are suitable precursors to azomethine ylides (e.g. **3**).

Application of this strategy to the synthesis of **1** would necessitate an intramolecular mode of the cycloaddition to access the bridged azatricyclo[5.3.0.0^{4,8}]decane core of the alkaloid. *N*-Benzyloxycarbonyl-L-glutamic acid-5-methyl ester (**5**)[11] was employed as a readily available starting material whose sole stereogenic center dictates the enantiospecific course of the synthesis (Scheme 2). Arndt–Eistert reaction of



Scheme 2. Reagents and conditions: a) EtOCOCl, Et_3N, THF, 0 °C; CH_2N_2, Et_2O, 87%; b) AgOAc, 1,4-dioxane, H_2O, 23 °C, 86%; c) EDCl, MeONHMe, Et_3N, $CHCl_3$, 23 °C, 89%; d) H_2, 10% Pd/C, MeOH, 23 °C, atmospheric pressure, 99%; e) NaH, $TMSCH_2Cl$, DMF, 23 °C, 49%; f) Lawesson's reagent (0.51 equiv), PhMe, 23 °C, 88%; g) $BrCH_2COEt$, then PPh_3, Et_3N, MeCN, 23 °C, 92%; h) CH≡CMgCl, THF, 0 °C; i) EtSH, Et_3N, CH_2Cl_2, 23 °C, 75%; j) Tf_2O (1.1 equiv), $CHCl_3$, 23 °C; TBAT (1.1 equiv), 65 °C, 24 h, 51%. EDCl = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, TMS = trimethylsilyl, DMF = *N*,*N*-dimethylformamide, Tf = trifluoromethanesulfonyl, TBAT = tetrabutylammonium triphenyldifluorosilicate.

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