ChemComm

Cite this: *Chem. Commun.*, 2011, **47**, 11639–11640

www.rsc.org/chemcomm

COMMUNICATION

Regio- and stereoselective synthesis of 1,4-dienes†

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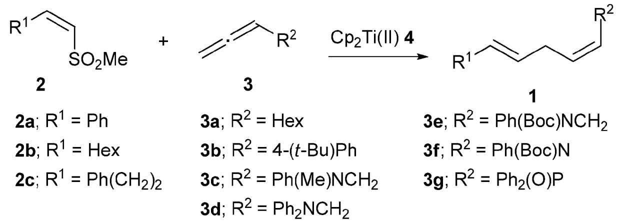
Received 2nd August 2011, Accepted 5th September 2011
DOI: 10.1039/c1cc14765j

Titanocene(II)-promoted cross-coupling between (*Z*)-alkenyl methyl sulfones and terminal allenes produced 1,4-dienes regioselectively *via* the formation of 2-alkylidenetitanacyclopentanes. Preferential formation of *E*,*Z*-dienes was observed in the reaction using aryl-, amino-, and phosphinylallenes.

Skipped dienes are important substructures in biological molecules and also valuable intermediates in organic synthesis. Therefore, a variety of methods for the preparation of 1,4-pentadienes have been reported.[1] Most investigated ways to construct such skipped dienes include the allylation of alkenylmetals[1a,e,g,n,s] and the transition metal-catalyzed 1,4-hydrovinylation of 1,3-dienes.[1f,k,l,o,p] Although preparations of 1,4-dienes by the low-valent titanium or zirconium-mediated cross-coupling of alkynes with allylic alcohols,[1i] allenic alcohols[1j] and allenes[1q] have been investigated, these reactions are disadvantageous in that high regioselectivity is achieved only when silylacethylenes are employed. Most of the foregoing methods are well applicable for the preparation of highly substituted 1,4-dienes, but there are only a few reports on the stereoselective preparation of unbranched 1,5-disubstituted 1,4-pentadienes. As for the preparation of such 1,4-dienes with *E*,*Z*-stereochemistry, the iridium-catalyzed cross-coupling of *o*-aminostyrene derivatives with allylic carbonates[1m] was studied. Recently, highly stereoselective preparation of 1,4-dienes by the titanium-mediated reductive cross-coupling of vinylcyclopropanes with alkynes was reported.[1t]

During the course of study on the titanocene(II)-promoted cross-coupling of unsaturated compounds *via* the formation of five-membered titanacycles,[2] we have found that (*Z*)-alkenyl sulfones are useful for the *E*-alkenylation of a variety of alkynes.[2b–d] The results prompted us to investigate the regio- and stereoselective preparation of 1,4-pentadienes **1** using (*Z*)-alkenyl sulfones **2** and terminal allenes **3** (Scheme 1).‡[3]

The treatment of 1,2-nonadiene (**3a**) with the alkenyl sulfone **2a** (2.6 equiv.) in the presence of the titanocene(II) reagent **4** (2.4 equiv.) in THF at 10 °C for 1 h gave the 1,5-disubstituted 1,4-pentadiene **1a** regioselectively as an almost 1 : 1 mixture of the stereoisomers (Table 1, entry 1). In contrast, the similar reaction of arylallene **3b** with **2a** proceeded with complete regio- and stereoselectivity to produce *E*,*Z*-pentadiene **1b** (entry 2).



Scheme 1

The observed regio- and stereoselectivity of the reaction is well explained by the formation of 2-alkylidenetitanacyclopentane intermediate **5** with retention of the configuration of alkenyl sulfone **2** (Scheme 2). Similarly to the reported alkenylation with (*Z*)-alkenyl sulfones **2**,[2b–d] the *syn*-elimination of the methylsulfonyl group results in the formation of an *E*-double bond. The stereochemistry of the double bond originated from allene **3** is rationalized by the relative stability of the titanacycle intermediates **5a** and **5b**. Unlike the reaction of the aliphatic allene **3a** (R^2 = Hex), the titanacycle intermediate **5b** would be largely destabilized by steric repulsion between R^2 and Cp rings when the arylallene **3b** (R^2 = 4-*tert*-butylphenyl) was employed. Hence, the *Z*-double bond was predominantly produced on hydrolysis of the alkenyltitanium species **6a** with retention of configuration.

Based on the above assumption, we further examined the reaction of functionalized allenes. As expected, good *Z*-selectivity was observed in the reaction using homoallenylamines (Table 1, entries 3, 4, 5, 8, 10). Furthermore, (1*Z*,4*E*)-1,4-pentadienylamines were obtained with complete stereoselectivity when allenylamines were employed (Table 1, entries 6, 9, 11).[4] The reaction of allenylphosphine oxide **3g** also produced the stereoisomerically pure 1,4-diene **1g** (Table 1, entry 7). All these results indicate that the stereochemistry of formation of titanacycle **5** is primarily determined by the steric interaction.

In conclusion, we have established the first straightforward method for the regio- and stereoselective preparation of linear *E*,*Z*-pentadienes by the titanocene(II)-promoted cross-coupling of (*Z*)-alkenyl sulfones with terminal allenes.[5] Further study on the extension of this new methodology is now under investigation.

This work was supported by Grant-in-Aid for Scientific Research (No. 21350026) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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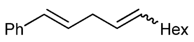
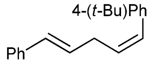
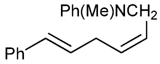
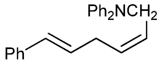
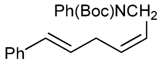
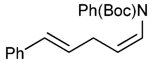
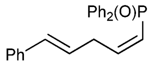
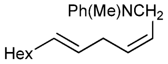
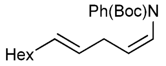
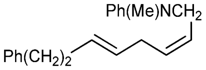
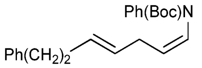
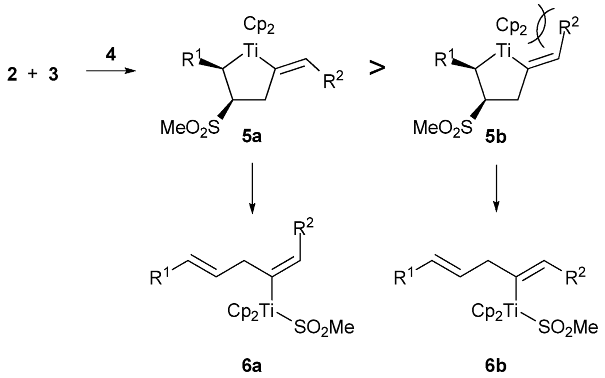
† Electronic supplementary information (ESI) available: All characterization data for 1,4-pentadienes **1**. See DOI: 10.1039/c1cc14765j

Table 1 Titanocene(II)-promoted cross-coupling of (*Z*)-alkenyl sulfones with terminal allenes

Entry	**2**	**3**	1,4-Diene **1**		Yield[a], % (*E*:*Z*)[b]
1	**2a**	**3a**		**1a**	76 (54:46)[c]
2	**2a**	**3b**		**1b**	74 (0:100)
3	**2a**	**3c**		**1c**	84 (14:86)
4	**2a**	**3d**		**1d**	89 (13:87)
5	**2a**	**3e**		**1e**	78 (25:75)
6	**2a**	**3f**		**1f**	88 (0:100)
7	**2a**	**3g**		**1g**	70 (0:100)
8	**2b**	**3c**		**1h**	82 (16:84)
9	**2b**	**3f**		**1i**	74 (0:100)
10	**2c**	**3c**		**1j**	80 (18:82)
11	**2c**	**3f**		**1k**	70 (0:100)

[a] Isolated yield based on allene **3** used. [b] The stereoisomeric ratio of the double bond originated from **3**. [c] The ratio of stereoisomers.



Scheme 2

Notes and references

‡ A typical experimental procedure is as follows: magnesium turnings (32 mg, 1.3 mmol), finely powdered molecular sieves 4A (120 mg) and Cp_2TiCl_2 (299 mg, 1.2 mmol) were placed in a flask and dried by heating with a heat gun under reduced pressure (2–3 mmHg). After cooling, THF (2 cm^3) and $P(OEt)_3$ (0.42 cm^3, 2.4 mmol) were added successively with stirring at 25 °C under Ar. After 3 h, the reaction mixture was cooled to 10 °C and then a THF (2 cm^3) solution of the alkenyl sulfone **2a** (237 mg, 1.3 mmol) was added dropwise over 10 min and stirring was continued for 15 min. A THF (10 cm^3) solution of the allene **3f** (116 mg, 0.5 mmol) was added to the reaction mixture over 2 h by using a syringe pump. Stirring was continued for further 1 h and then the reaction was quenched with 1 M NaOH. The insoluble materials were filtrated off through Celite and washed with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. After the combined organic extracts were dried over Na_2SO_4, the solvent was removed under reduced pressure and the residue was purified by alumina gel column chromatography (eluted with hexane/AcOEt (95:5) containing a trace amount of hydroquinone) to give **1f** (148 mg, 88%); ν_{max} (neat)/cm^{-1} 3060, 3028, 2978, 2930, 1712, 1657, 1495, 1323, 1302, 1254, 1165, 740 and 693; δ_H (300 MHz, $CDCl_3$; Me_4Si) 1.47 (s, 9H), 2.45 (dd, J = 7.5, 6.5 Hz, 2H), 5.00 (dt, J = 8.7, 7.5 Hz, 1H), 5.87 (dt, J = 15.9, 6.5 Hz, 1H), 6.10 (d, J = 15.9 Hz, 1H), 6.55 (d, J = 8.7 Hz, 1H) and 7.14–7.39 (m, 10H); δ_C (75 MHz; $CDCl_3$) 28.2, 30.0, 81.3, 117.5, 125.8, 125.9, 126.7, 126.9, 127.5, 128.1, 128.4, 128.6, 130.3, 137.5, 141.9 and 153.4; m/z (FAB) 334.1809 [$(M - H)^+$] ($C_{22}H_{24}NO_2$ requires 334.1802).

1 For recent examples, see: (*a*) H. Taguchi, K. Ghoroku, M. Tadaki, A. Tsubouchi and T. Takeda, *J. Org. Chem.*, 2002, **67**, 8450; (*b*) A. N. Thadani and V. H. Rawal, *Org. Lett.*, 2002, **4**, 4317; (*c*) D. C. Braddock and A. Matsuno, *Synlett*, 2004, 2521; (*d*) D. C. Braddock, D. M. Badine, T. Gottschalk, A. Matsuno and M. Rodriguez-Lens, *Synlett*, 2003, 345; (*e*) Y. Kayaki, T. Koda and T. Ikariya, *Eur. J. Org. Chem.*, 2004, 4989; (*f*) A. Zhang and T. V. Rajan Babu, *J. Am. Chem. Soc.*, 2006, **128**, 54; (*g*) G. W. Kabalka and M. Al-Masum, *Org. Lett.*, 2006, **8**, 11; (*h*) G. Hilt and J. Treutwein, *Angew. Chem., Int. Ed.*, 2007, **46**, 8500; (*i*) F. Kolundzic and G. C. Micalizio, *J. Am. Chem. Soc.*, 2007, **129**, 15112; (*j*) H. L. Shimp, A. Hare, M. McLaughlin and G. C. Micalizio, *Tetrahedron*, 2008, **64**, 3437; (*k*) B. Moreau, J. Y. Wu and T. Ritter, *Org. Lett.*, 2009, **11**, 337; (*l*) G. Hilt and J. Treutwein, *Chem. Commun.*, 2009, 1395; (*m*) H. He, W.-B. Liu, L.-X. Dai and S.-L. You, *J. Am. Chem. Soc.*, 2009, **131**, 8346; (*n*) K. Akiyama, F. Gao and A. H. Hoveyda, *Angew. Chem., Int. Ed.*, 2010, **49**, 419; (*o*) R. K. Sharma and T. V. Rajan Babu, *J. Am. Chem. Soc.*, 2010, **132**, 3295; (*p*) M. Arndt, A. Reinhold and G. Hilt, *J. Org. Chem.*, 2010, **75**, 5203; (*q*) W. Zheng, Y. Wu, F. Zheng, L. Hu and Y. Hong, *Tetrahedron Lett.*, 2010, **51**, 4702; (*r*) W.-B. Liu, H. He, L.-X. Dai and S.-L. You, *Chem.–Eur. J.*, 2010, **16**, 7376; (*s*) F. Gao, K. P. McGrath, Y. Lee and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2010, **132**, 14315; (*t*) T. K. Macklin and G. C. Micalizio, *Nat. Chem.*, 2010, **2**, 638.

2 (*a*) A. Ogata, M. Nemoto, K. Arai, K. Kobayashi, A. Tsubouchi and T. Takeda, *Eur. J. Org. Chem.*, 2006, 878; (*b*) A. Ogata, M. Nemoto, K. Kobayashi, A. Tsubouchi and T. Takeda, *J. Org. Chem.*, 2007, **72**, 3816; (*c*) A. Ogata, M. Nemoto, K. Kobayashi, A. Tsubouchi and T. Takeda, *Chem.–Eur. J.*, 2007, **13**, 1320; (*d*) A. Ogata, M. Nemoto, Y. Takano, A. Tsubouchi and T. Takeda, *Tetrahedron Lett.*, 2008, **49**, 3071; (*e*) S. Oishi, K. Ohomika, A. Tsubouchi and T. Takeda, *Chem. Lett.*, 2010, **39**, 723.

3 The (*Z*)-alkenyl sulfones **2** were prepared by the DIBAL reduction[a] of alkynyl sulfides[b] followed by oxidation with oxone®; (*a*) M. J. Dabdoub and P. G. Guerrero Jr., *Tetrahedron Lett.*, 2001, **42**, 7167; (*b*) H. A. Stefani, R. Cella, F. A. Dörr, C. M. P. de Pereira, F. P. Gomes and G. Zeni, *Tetrahedron Lett.*, 2005, **46**, 2001. Homoallenylamines **3c**, **3d**, **3e** were obtained by the reaction of propargylamines with paraformaldehyde in the presence of diisopropylamine and copper(I) bromide; S. Searles, Y. Li, B. Nassim, M. R. Lopes, P. T. Tran and P. Crabbé, *J. Chem. Soc., Perkin Trans. 1*, 1984, 747. The allenylamine **3f** was prepared by isomerization of the corresponding propargylamine with *t*-BuOK in THF at −78 °C for 30 min; for example, see: F. Le Strat and J. Maddaluno, *Org. Lett.*, 2002, **4**, 2791. The allenylic diphenyl phosphine oxide **3g** was synthesized by the reaction of propargyl alcohol with Ph_2PCl in the presence of Et_3N; H. Guo, R. Qian, Y. Guo and S. Ma, *J. Org. Chem.*, 2008, **73**, 7934.

4 For the stereoselective preparation of (1*E*,4*E*)-1,4-pentadienylamines, see: B. M. Trost and J.-P. Surivet, *Angew. Chem., Int. Ed.*, 2001, **40**, 1468.

5 Similarly to the alkenylation of alkynes,[2b] (*E*)-alkenyl sulfones are ineffective for the alkenylation of allenes; the reaction of *E*-enriched **2a** (*E*:*Z* = 73:27) with **3c** produced **1c** only in a poor yield (10%; *E*:*Z* = 11:89) and a substantial amount of *E*-**2a** was recovered.