ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2014, **50**, 808

Received 13th July 2013,
Accepted 5th November 2013

DOI: 10.1039/c3cc45286g

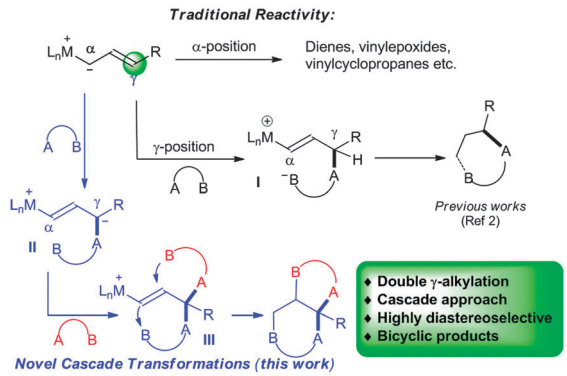
www.rsc.org/chemcomm

Double γ-alkylation of allylic phosphorus ylides: a unique access to oxa-bicyclic[3.3.0] diene skeletons†

Peng Wang, Saihu Liao, Jian-Bo Zhu and Yong Tang*

A new ylide-initiated tandem cyclization reaction based on γ-dialkylation of allylic ylides has been realized, delivering a series of [3.3.0] oxa-bicyclic dienes in high yields with perfect diastereoselectivity.

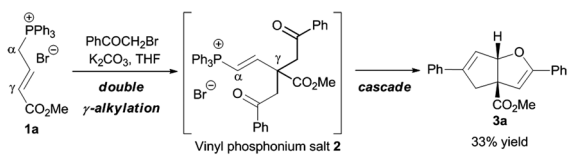
In the last decade, the development of cascade reactions has attracted considerable research interest, due to their competences and efficiency in the fast enrichment of molecular complexity, which are especially prominent in the construction of polycyclic frameworks.[1] Recently, along with our exploration of novel ylide cyclization reactions,[2] allylic ylides were identified as versatile reactants, which can readily participate in a variety of ylide-initiated Michael addition cyclization (YIMAC) reactions, providing novel and efficient approaches to cyclic and polycyclic products.[2–4] Typically, a YIMAC reaction cascade was triggered by the addition of the γ-carbon of the allylic ylides to a Michael acceptor. This is in contrast to the traditional reactivity of allylic ylides which normally leads to dienes,[5] small ring compounds[6] *etc.* upon the reactions at the α-position of allylides. In a typical YIMAC reaction, the γ-alkylation happens first to generate intermediate I, followed by ring-closure to deliver the final cyclic products.[2] In view of intermediate I that contains an electrophilic vinyl function and an acidic γ proton, it is speculated that its γ-deprotonation would produce a new allylic ylide (intermediate II, Scheme 1), which can probably react with the second electrophile (A and B) at the γ position to afford intermediate III. Eventually, by virtue of an intramolecular addition–ylide reaction cascade, a bicyclic product can be forged, providing a simple way to construct complex skeletons. However, to the best of our knowledge, a few examples were reported probably due to the challenge of *in situ* dual substitutions at the γ-position of allylic ylide to form quaternary carbon. In this communication, we wish to report our effort on this subject.



Scheme 1 Reaction types of allylic ylides.

Very recently, we developed a domino process for the synthesis of cyclopentadiene products, and luckily isolated a key phosphonium salt intermediate which resulted from a cyclopropanation–ring-opening–alkylation cascade of an allylic ylide and on the other hand can also be regarded as the product of a formal γ-dialkylation of the allylic phosphorus ylide.[7] This result suggests that double γ-alkylation of an allylic ylide is possible and can probably be employed as an impetus in tandem reaction design. To our great pleasure, by using 2-bromoacetophenone as an alkylating reagent, a type of product with an oxa-bicyclic[3.3.0] diene framework was isolated (Scheme 2), which was further confirmed by X-ray analysis of **3f** (for details, please see ESI†).[10] This structure is widely found in natural products and resembles Lin's diene ligands.[8]

Initially, the double γ-alkylation cascade reaction of allylic phosphonium salt **1a** with 2-bromoacetophenone was performed in THF at room temperature. The influences of bases and solvents were

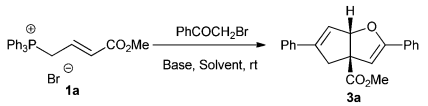


Scheme 2 Double γ-dialkylation to oxa-bicyclic[3.3.0] dienes.

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China. E-mail: tangy@sioc.ac.cn

† Electronic supplementary information (ESI) available: Experimental data, spectra, and crystallographic data. CCDC 931337, 931342 and 931343. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc45286g

Table 1 Base and solvent effects



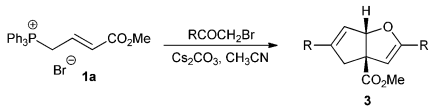
Entry[a]	Base	Solvent	Yield[b] (%)
1	NaH	THF	<1
2	CH_3ONa	THF	<1
3	*t*-BuOK	THF	<1
4	Na_2CO_3	THF	<1
5	K_2CO_3	THF	33
6	Cs_2CO_3	THF	75
7	Cs_2CO_3	DCM	94
8	Cs_2CO_3	DCE	88
9	Cs_2CO_3	i-PrOAc	61
10	Cs_2CO_3	CH_3CN	87
11	Cs_2CO_3	DMSO	80
12[c]	Cs_2CO_3	CH_3CN	95
13[c]	Cs_2CO_3	DCM	94

[a] Phosphonium salt **1a** (176.4 mg, 0.4 mmol), $PhCOCH_2Br$ (159.2 mg, 0.80 mmol), 17 h. [b] Isolated yield. [c] Phosphonium salt **1a** (176.4 mg, 0.4 mmol), $PhCOCH_2Br$ (199 mg, 1.0 mmol).

first investigated. As shown in Table 1, strong bases such as NaH, MeONa, *t*-BuOK led to only a trace amount of the desired product (entries 1–3); severe decomposition of bromide was observed in these cases. Interestingly, the transformation completely halted at the double alkylation stage when Na_2CO_3 was used as a base, and the salt was isolated in a quantitative yield (entry 4, Table 1). Fortunately, Cs_2CO_3 was especially effective for this reaction, yielding the desired product as a single diastereoisomer in 75% yield (entry 6, Table 1). With respect to the solvent effect, halogenated solvents in general afforded better results, and DCM was identified the best (94% yield, entry 7). Other polar solvents such as CH_3CN and DMSO were also suitable, giving 87% and 80% yields, respectively. In addition, increasing the amount of 2-bromoacetophenone from 2.0 to 2.5 equivalents could improve the yield of the reaction in CH_3CN to 95% (entry 12, Table 1), while adding another 0.5 equivalent of 2-bromoacetophenone led to no further improvement when DCM was used as the reaction media (entry 13, Table 1).

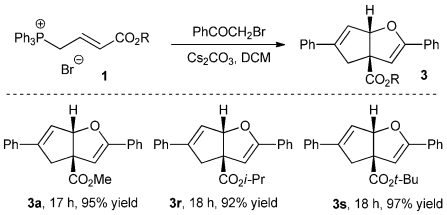
Under the optimized reaction conditions, the reaction scope was examined next. As shown in Table 2, aryl, heteroaryl, and alkyl α-bromoketones, all are suitable substrates. And functional groups such as ether, halide, nitro, trifluoromethyl, and nitrile were also well tolerated in the current reaction. In general, better yields were obtained with substrates containing a *para* electron-donating group at the benzene ring than those attached with an electron-withdrawing group (entries 2–6 *vs.* 7–9). Regarding the substitution pattern, the yield of *ortho* bromo-substituted bromide was decreased by *ca.* 10%, in comparison to the *meta* and *para*-substituted ones (entry 11 *vs.* entries 6 and 12). Notably, alkyl substrate 1-bromobutan-2-one was also compatible under the current conditions, delivering the alkyl substituted bicyclic diene in 68% yield. Moreover, substrates such as 2-benzofuranyl and 4-pyridyl α-bromoketones also readily participated in the tandem reaction (entries 15 and 16). On the other hand, variation on the ester group led to a similar result (Scheme 3). In addition, the use of a chiral ester derived from (−)-8-phenylmenthol could induce 20% diastereomeric excess.

Table 2 Scope and limitation

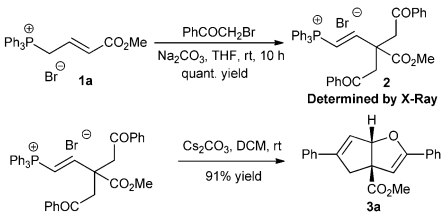


Entry[a]	R	t^b (h)	Yield[c] (%)
1	Ph- (**3a**)	17	95
2	*p*-$MeOC_6H_4$- (**3b**)	36	89
3	*p*-MeC_6H_4- (**3c**)	36	95
4	*p*-FC_6H_4- (**3d**)	36	96
5	*p*-ClC_6H_4- (**3e**)	36	98
6	*p*-BrC_6H_4- (**3f**)	24	95
7	*p*-$NO_2C_6H_4$- (**3g**)	19	69
8	*p*-$CF_3C_6H_4$- (**3h**)	20	86
9	*p*-CNC_6H_4- (**3i**)	24	65
10	3,4-$Cl_2C_6H_3$- (**3j**)	24	74
11	*o*-BrC_6H_4- (**3k**)	24	82
12	*m*-BrC_6H_4- (**3l**)	24	91
13	2-Naphthyl- (**3m**)	24	92
14	Et- (**3n**)	37	68
15	2-Benzofuryl (**3o**)	36	39
16[d]	4-Pyridyl (**3p**)	37	46

[a] Conditions: phosphonium salt **1a** (176.4 mg, 0.4 mmol), $RCOCH_2Br$ (1.0 mmol), Cs_2CO_3 (522.0 mg, 1.6 mmol), CH_3CN (8.0 mL), RT. [b] The reaction time was not optimized. [c] Isolated yield. [d] 2-Bromo-1-(4-pyridinyl)-1-ethanone hydro-bromide was used.



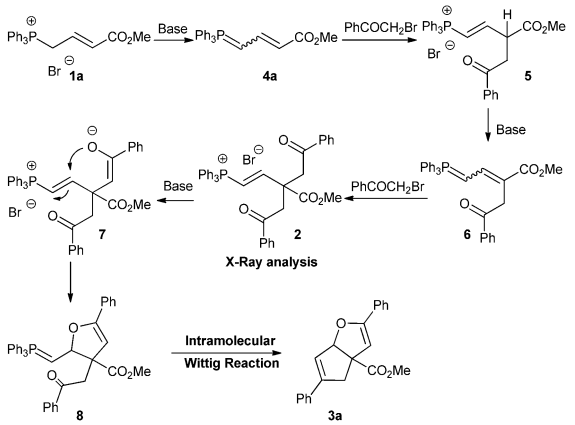
Scheme 3 Ester effects on this reaction.



Scheme 4 Isolation of intermediate **2** and its conversion to **3a**.

To our delight, a key intermediate, vinyl phosphonium salt **2**, was isolated in quantitative yield when Na_2CO_3 was used as the base (Scheme 4). The structure of **2** was further confirmed by the X-ray single crystal analysis (for more information, see ESI†).[10] Subjecting the intermediate to the standard reaction conditions afforded oxa-bicyclic[3.3.0] diene **3a** in 91% yield, suggesting that the double γ-alkylation did occur and vinyl phosphonium salt **2** was a key intermediate in this tandem process.

Based on the above results, a plausible mechanism was proposed (Scheme 5). γ-Dialkylation of allylic phosphorus ylide **4a** derived from **1a** delivers the key intermediate, vinyl phosphonium salt **2**, which has been successfully isolated and characterized.[9] Then, a base-promoted deprotonation of the alpha proton of **2**



Scheme 5 Plausible reaction pathway.

affords enolate 7, and the intramolecular oxa-addition–Wittig cascade furnishes the final oxa-bicyclic diene products.

Furthermore, the single alkylation phosphonium salt **5** was isolated (Scheme 5), and treated with other electrophiles such as cinnamyl bromide, nitroolefins, 2-chloroacetamide. However, a complex mixture was obtained in all cases except the nitrostyrene, with a 23% yield of the double alkylation product. When two different α-bromo ketones were used, a complex mixture was also afforded, probably because the racemic phosphonium salt **2** provides diverged enolates 7 and the cyclization of the enolates 7 derived from different ketones gives a mixture.

Apart from their presence in natural products, the oxa-bicyclic[3.3.0] diene skeletons also possess a concave structure resembling Lin's diene ligand.[8] We thus prepared the complex $[RhCl(\mathbf{3a})]_2$ using as $[RhCl(C_2H_4)_2]_2$ a precursor (Scheme 5).

In conclusion, a novel cascade reaction based on γ-dialkylation of allylic phosphorus ylides has been successfully developed for the first time. The reaction provides a facile and efficient approach for the synthesis of oxa-bicyclic[3.3.0] diene compounds with perfect diastereoselectivity. An Rh–diene complex has also been successfully synthesized and characterized. The asymmetric version of the current reaction is underway in our laboratory and will be reported in due course.

We are grateful for the financial support from the Natural Science Foundation of China (No. 20932008, 21121062, 21272248), the Major State Basic Research Development Program (Grant No. 2009CB825300) and Chinese Academy of Sciences.

Notes and references

1 For reviews about tandem/cascade/domino reactions, see: (*a*) H. Pellissier, *Chem. Rev.*, 2013, **113**, 442–524; (*b*) H. Claviera and H. Pellissier, *Adv. Synth. Catal.*, 2012, **354**, 3347–3403; (*c*) H. Pellissier, *Adv. Synth. Catal.*, 2012, **354**, 237–294; (*d*) A. Grossmann and D. Enders, *Angew. Chem., Int. Ed.*, 2012, **51**, 314–325; (*e*) C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.*, 2010, **2**, 167–178; (*f*) J. Zhou, *Chem.–Asian J.*, 2010, **5**, 422–434; (*g*) J. Barluenga, F. Rodríguez and F. J. Fañanás, *Chem.–Asian J.*, 2009, **4**, 1036–1048; (*h*) D. Enders, C. Grondal and M. R. M. Hüttl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570–1581; (*i*) K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem., Int. Ed.*, 2006, **45**, 7134–7186; (*j*) K. C. Nicolaou and J. S. Chen, *Chem. Soc. Rev.*, 2009, **38**, 2993–3009; (*k*) P. J. Parsons, C. S. Penkett and A. J. Shell, *Chem. Rev.*, 1996, **96**, 195–206; (*l*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115–136; (*m*) I. Ryu and N. Sonoda, *Chem. Rev.*, 1996, **96**, 177–194.

2 For accounts, see: (*a*) X.-L. Sun and Y. Tang, *Acc. Chem. Res.*, 2008, **41**, 937–948; (*b*) Y. Tang, S. Ye and X.-L. Sun, *Synlett*, 2005, 2720–2730. For selected examples, see: (*c*) J.-B. Zhu, P. Wang, S. Liao and Y. Tang, *Chem. Commun.*, 2013, **49**, 4570–4572; (*d*) Q.-G. Wang, S.-F. Zhu, L.-W. Ye, C.-Y. Zhou, X.-L. Sun, Y. Tang and Q.-L. Zhou, *Adv. Synth. Catal.*, 2010, **352**, 1914–1919; (*e*) L.-W. Ye, S.-B. Wang, Q.-G. Wang, X.-L. Sun, Y. Tang and Y.-G. Zhou, *Chem. Commun.*, 2009, 3092–3094; (*f*) Q.-G. Wang, X.-M. Deng, B.-H. Zhu, L.-W. Ye, X.-L. Sun, C.-Y. Li, C.-Y. Zhu, Q. Shen and Y. Tang, *J. Am. Chem. Soc.*, 2008, **130**, 5408–5409; (*g*) L.-W. Ye, X.-L. Sun, Q.-G. Wang and Y. Tang, *Angew. Chem., Int. Ed.*, 2007, **46**, 5951–5954.

3 For recent accounts and works on tandem ylide reactions by other contributors, see: (*a*) L.-Q. Lu, J.-R. Chen and W.-J. Xiao, *Acc. Chem. Res.*, 2012, **45**, 1278–1293; (*b*) Y. Cheng, X.-Q. Hu, S. Gao, L.-Q. Lu, J.-R. Chen and W.-J. Xiao, *Tetrahedron*, 2013, **69**, 3810–3816; (*c*) P. Xie, E. Li, J. Zheng, X. Li, Y. Huang and R. Chen, *Adv. Synth. Catal.*, 2013, **355**, 161–169; (*d*) Q.-Q. Yang, C. Xiao, L.-Q. Lu, J. An, F. Tan, B.-J. Li and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2012, **51**, 9137–9140; (*e*) P. Xie, Y. Huang and R. Chen, *Chem.–Eur. J.*, 2012, **18**, 7362–7366; (*f*) L.-Q. Lu, F. Li, J. An, Y. Cheng, J.-R. Chen and W.-J. Xiao, *Chem.–Eur. J.*, 2012, **18**, 4073–4079; (*g*) L.-Q. Lu, F. Li, J. An, J.-J. Zhang, X.-L. An, Q.-L. Hua and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2009, **48**, 9542–9545; (*h*) M. G. Unthank, B. Tavassoli and V. K. Aggarwal, *Org. Lett.*, 2008, **10**, 1501–1504; (*i*) M. G. Unthank, N. Hussain and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2006, **45**, 7066–7069; (*j*) C. C. C. Johansson, N. Bremeyer, S. V. Ley, D. R. Owen, S. C. Smith and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2006, **45**, 6024–6028; (*k*) N. Bremeyer, S. C. Smith, S. V. Ley and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2004, **43**, 2681–2684.

4 For reviews about phosphine-catalyzed cyclization *via* ylide path, see: (*a*) T.-Y. Liu, M. Xie and Y.-C. Chen, *Chem. Soc. Rev.*, 2012, **41**, 4101–4112; (*b*) A. Marinetti and A. Voituriez, *Synlett*, 2010, 174–194; (*c*) B. J. Cowen and S. J. Miller, *Chem. Soc. Rev.*, 2009, **38**, 3102–3116; (*d*) L.-W. Ye, J. Zhou and Y. Tang, *Chem. Soc. Rev.*, 2008, **37**, 1140–1152; (*e*) X. Lu, Y. Du and C. Lu, *Pure Appl. Chem.*, 2005, **77**, 1985–1990; (*f*) J. L. Methot and W. R. Roush, *Adv. Synth. Catal.*, 2004, **346**, 1035–1050; (*g*) X. Lu, C. Zhang and Z. Xu, *Acc. Chem. Res.*, 2001, **34**, 535–544.

5 For accounts about olefination of allylic ylide, see: (*a*) B. E. Maryanoff and A. B. Reitz, *Chem. Rev.*, 1989, **89**, 863–927; (*b*) P. J. Murphy, *Chem. Soc. Rev.*, 1988, **17**, 1–30; (*c*) S. Xu, R. Chen and Z. He, *J. Org. Chem.*, 2011, **76**, 7528–7538; (*d*) T. Wang, L.-T. Shen and S. Ye, *Synthesis*, 2011, 3359–3363; (*e*) S. Xu, L. Zhou, S. Zeng, R. Ma, Z. Wang and Z. He, *Org. Lett.*, 2009, **11**, 3498–3501.

6 For reviews about synthesis of small ring compounds using allylic ylides, see: (*a*) Y. Tang, S. Ye, Z.-Z. Huang and Y.-Z. Huang, *Heteroat. Chem.*, 2002, **13**, 463–466; (*b*) Y.-Z. Huang, Y. Tang and Z.-L. Zhou, *Tetrahedron*, 1998, **54**, 1667–1690; (*c*) L.-X. Dai, X.-L. Hou and Y.-G. Zhou, *Pure Appl. Chem.*, 1999, **71**, 369–376; (*d*) A.-H. Li, L.-X. Dai and V. K. Aggarwal, *Chem. Rev.*, 1997, **97**, 2341–2372.

7 (*a*) S. R. Wang, C.-Y. Zhu, X.-L. Sun and Y. Tang, *J. Am. Chem. Soc.*, 2009, **131**, 4192–4193; (*b*) P. Wang, L. Lin, J.-B. Zhu, S.-H. Liao, S. R. Wang, Y.-X. Li and Y. Tang, *Chem.–Eur. J.*, 2013, **19**, 6766–6773; (*c*) P. Wang, S. Liao, J.-B. Zhu and Y. Tang, *Org. Lett.*, 2013, **15**, 3606–3609; (*d*) P. Wang, S. Liao, S. R. Wang, R.-D. Gao and Y. Tang, *Chem. Commun.*, 2013, **49**, 7436–7438.

8 (*a*) C.-G. Feng, M.-H. Xu and G.-Q. Lin, *Synlett*, 2011, 1345–1356; (*b*) Y.-X. Liao, C.-R. Xing and Q.-S. Hu, *Org. Lett.*, 2012, **14**, 1544–1547; (*c*) Z. Cui, H.-J. Yu, R.-F. Yang, W.-Y. Gao, C.-G. Feng and G.-Q. Lin, *J. Am. Chem. Soc.*, 2011, **133**, 12394–12397; (*d*) C. Shao, H.-J. Yu, N.-Y. Wu, C.-G. Feng and G.-Q. Lin, *Org. Lett.*, 2010, **12**, 3820–3823; (*e*) S.-S. Zhang, Z.-Q. Wang, M.-H. Xu and G.-Q. Lin, *Org. Lett.*, 2010, **12**, 5546–5549; (*f*) C.-G. Feng, Z.-Q. Wang, P. Tian, M.-H. Xu and G.-Q. Lin, *Chem.–Asian J.*, 2008, **3**, 1511–1516; (*g*) S. Helbig, S. Sauer, N. Cramer, S. Laschat, A. Baro and W. Freya, *Adv. Synth. Catal.*, 2007, **349**, 2331–2337; (*h*) Z.-Q. Wang, C.-G. Feng, M.-H. Xu and G.-Q. Lin, *J. Am. Chem. Soc.*, 2007, **129**, 5336–5337.

9 (*a*) M. Hatanaka, Y. Himeda, Y. Tanaka and I. Ueda, *Tetrahedron Lett.*, 1995, **36**, 3211–3214; (*b*) M. Hatanaka, Y. Himeda, R. Imashiro, Y. Tanaka and I. Ueda, *J. Org. Chem.*, 1994, **59**, 111–119; (*c*) M. Hatanaka, Y. Himeda and I. Ueda, *Tetrahedron Lett.*, 1991, **32**, 4521–4524.

10 CCDC 931337 (**3f**), CCDC 931342 (**2**) and CCDC 931343 (**3a**/Rh), also see ESI†.

