CuI-catalyzed intramolecular *O*-vinylation of carbonyl compounds†

Yewen Fang and Chaozhong Li*

Received (in Cambridge, UK) 11th April 2005, Accepted 11th May 2005
First published as an Advance Article on the web 1st June 2005
DOI: 10.1039/b505006e

The first copper-catalyzed intramolecular *O*-vinylation of carbonyl compounds with vinyl bromides was reported, among which the efficient formation of 5-, 6- and even 7-membered cyclic alkenyl ethers was achieved with β-ketoesters as nucleophiles.

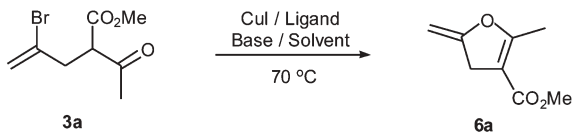
Cyclic alkenyl ethers are important building blocks in organic synthesis. They also constitute a class of natural products possessing significant biological properties.[1] Preparations of cyclic alkenyl ethers have received much attention and continue to be actively pursued. However, very few successful reports have been documented.[2,3] Among them, the transition metal-catalyzed intramolecular addition of an oxygen functionality to a carbon–carbon triple bond has drawn a great deal of interest.[3] We here report that Cu(I)-catalyzed intramolecular *O*-vinylation of ketones with vinyl bromides provides a convenient and efficient route for the synthesis of cyclic alkenyl ethers.

The formation of aromatic C–X bonds (X = N, O, S, *etc.*) *via* copper-catalyzed coupling between arylhalides and hetero-centered nucleophiles has attracted considerable attention during the past few years.[4,5] The high stability and low costs of the copper catalysts enable these transformations to be a useful complement to the more extensively studied palladium-catalyzed processes.[4c,6] This methodology was successfully extended to the vinylation of amides or carbamates[7] and, more recently, to the *O*-vinylation[8] of alcohols and phenols with vinyl iodides or bromides as the vinyl source. It could be envisioned that, if the *O*-vinylation could be carried out intramolecularly, it might provide a facile route to the synthesis of cyclic alkenyl ethers. Due to the importance of cyclic alkenyl ethers in organic synthesis, we carried out the following investigation to explore the scope and limitation of this possible methodology.

We chose the following three compounds of typical structural features as the model substrates, bromoenol **1** and bromoenones **2** and **3a**. The choice of bromo-substituted compounds rather than their iodine-analogs was in an endeavor to make the method more synthetically valuable. Following Buchwald's method,[8a] the substrates were subjected to the treatment of 20 mol% of CuI and 40 mol% of *N*,*N*′-dimethylethylenediamine (**A**) with K_2CO_3 (2 equiv) as the base in THF at refluxing temperature. The results are summarized in Table 1. The reaction of bromoenol **1** proceeded sluggishly. After 24 h, the cyclized product **4** was isolated in 35% yield along with a significant amount of **1** recovered (entry 1, Table 1). Changing the base from K_2CO_3 to *t*-BuOK yielded a complicated mixture that was difficult to characterize (entry 2, Table 1).

With bromoenone **2**, the reaction was also very slow and a large amount of starting material remained unchanged after 24 hours at reflux in THF. The furan product **5** was isolated in 22% yield (entry 3, Table 1). Apparently the expected cyclization product with an exocyclic C=C double bond underwent isomerization to the more stable furan form. Raising the reaction temperature to about 100 °C (with dioxane as the solvent) resulted in a slight improvement of yield (41%). Use of the stronger base *t*-BuOK in THF was not helpful (entry 5, Table 1).

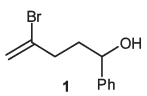
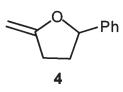
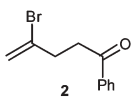
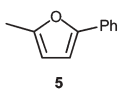
Although there is still room to optimize the experimental conditions in the reactions of **1** or **2**, we turned our attention to substrate **3a** and found that much better results could be achieved (eqn. (1)



3a **6a** (1)

and Table 2).‡ With K_2CO_3 as the base, the treatment of **3a** with 10 mol% of CuI and 20 mol% of ligand **A** in THF for 1 h led to the formation of the cyclized product **6a** in almost quantitative yield (entry 1, Table 2). Reducing the amount of CuI to 5 mol% afforded the product in 93% yield within 2 h (entries 2 and 3, Table 2). The cyclization also proceeded without the ligand **A**, albeit in a longer reaction time, while no reaction occurred in the absence of the copper catalyst (entries 4 and 5, Table 2). These results illustrated that CuI is required and diamine **A** significantly accelerates the reaction. Further controlled experiments showed

Table 1 CuI-catalyzed reactions of **1** and **2**[a]

Entry	Substrate	Solvent	Base	Product	Yield (%)[b]
1	 **1**	THF	K_2CO_3	 **4**	35
2	**1**	THF	*t*-BuOK	—	—
3	 **2**	THF	K_2CO_3	 **5**	22
4	**2**	dioxane	K_2CO_3	**5**	41
5	**2**	THF	*t*-BuOK	**5**	34

[a] Experimental conditions: CuI (20 mol%), **A** (40 mol%), base (2 equiv.), solvent (0.1 M), reflux for 24 h. [b] Isolated yield based on **1** or **2**.

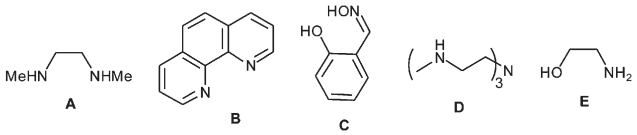
† Electronic supplementary information (ESI) available: characterization of compounds **1–11**. See http://www.rsc.org/suppdata/cc/b5/b505006e/

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, P. R. China.
E-mail: clig@mail.sioc.ac.cn; Fax: +86-21-6416-6128
*clig@mail.sioc.ac.cn

Table 2 Synthesis of **6a** from **3a**

Entry	CuI (mol%)	Ligand[a]	Base	Solvent	Time (h)[b]	Yield (%)[c]
1	10	**A**	K_2CO_3	THF	1	95
2	5	**A**	K_2CO_3	THF	1	79
3	5	**A**	K_2CO_3	THF	2	93
4	10	None	K_2CO_3	THF	5	87
5	0	None	K_2CO_3	THF	5	0
6	5	**B**	K_2CO_3	THF	1	24
7	5	**C**	K_2CO_3	THF	1	23
8	5	**D**	K_2CO_3	THF	1	30
9	5	**E**	K_2CO_3	THF	1	43
10	5	**A**	Cs_2CO_3	THF	2	94
11	5	**A**	Na_2CO_3	THF	2	46
12	5	**A**	Et_3N	THF	2	42
13	5	**A**	K_2CO_3	dioxane	2	83

[a] Ligand:CuI = 2:1. [b] Experimental conditions: CuI, ligand, base (2 equiv.), solvent (0.1 M), reflux. [c] Isolated yield based on **3a**.

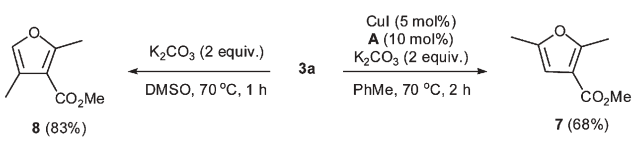


Scheme 1 Ligands screened.

that diamine **A** was superior over other frequently used ligands **B** to **E** (entries 2 and 6–9, Table 2, Scheme 1). We then compared K_2CO_3 with other bases (entries 10–12, Table 2). Cs_2CO_3 showed the same effect as K_2CO_3, while Na_2CO_3 or Et_3N were much less satisfactory. The cyclization also proceeded well in dioxane (entry 13, Table 2). However, when toluene was used as the solvent, the isomerized product, furan **7**, was isolated. Moreover, heating **3a** with K_2CO_3 in DMSO or DMF led to the formation of the rearrangement product furan **8**, indicating that DMSO and DMF are not solvents of choice (Scheme 2).[9]

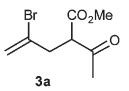
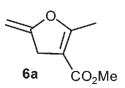
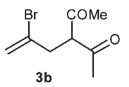
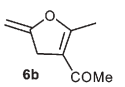
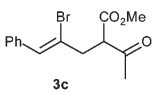
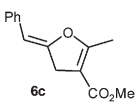
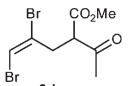
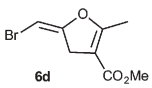
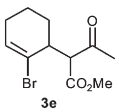
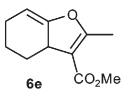
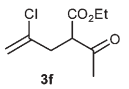
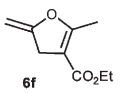
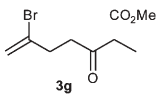
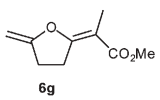
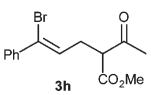
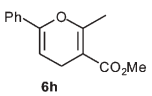
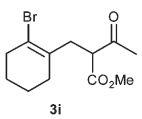
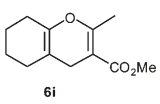
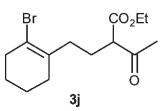
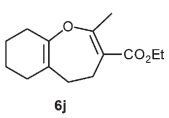
The different behavior described above between **3a** and **2** might be attributed to the much easier enolation of **3a** as a β-ketoester. It is worth mentioning that Suzuki and coworkers reported the intermolecular reactions of cyclic 1,3-dicarbonyl compounds with vinyl bromides in HMPA in the presence of an equimolar amount of CuI in which *C*-alkylation occurred rather than *O*-vinylation.[10]

Based on the above results, a number of bromoenones **3a–j** were prepared and subjected to the treatment of CuI (5 mol%), diamine **A** (10 mol%) and K_2CO_3 (2 equiv.) in THF at refluxing temperature. The results are presented in Table 3. The corresponding 5-membered cyclic alkenyl ethers **6a–e** were achieved in high yield in a short time (entries 1–5, Table 3). The reaction was efficient with di-, tri- and tetra-substituted vinyl bromides and the complete retention of configuration at the double bond was observed. Vinyl chloride was also effective, although a longer reaction time was required (entry 6, Table 3). Moreover, the cyclization of compound **3g** afforded tetrahydrofuran product **6g**



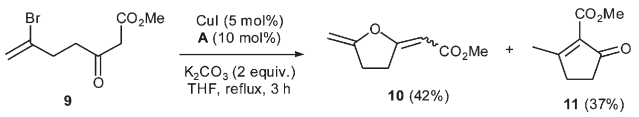
Scheme 2

Table 3 Synthesis of cyclic alkenyl ethers **6a–j**

Entry	Substrate	Time (h)	Product	Yield (%)[a]
1		2		89
2		2		86
3		4		91
4		1		92
5		2		92
6		8		99
7		1		99
8		16		86
9		4		99
10		48		83

[a] Isolated yield based on **3**.

with two exocyclic double bonds with an excellent stereoselectivity as evidenced by its NOESY experiment (entry 7, Table 2). As a comparison, the reaction of a similar substrate **9** produced a mixture of the *C*-vinylation product **11** and the *O*-vinylation product **10** with poor stereoselectivity (Z:E ~ 1:2) (Scheme 3). The reason for the different behavior between **3g** and **9** is unclear.



Scheme 3

It is noteworthy that similar compounds to **6a–g** were postulated but not isolated as the intermediates in the synthesis of furans *via* transition metal-catalyzed cyclization of alkynols.[3] The successful isolation of compounds **6a–g** also indicated the mildness of the above reaction conditions.

We then extended this method to the synthesis of 6-membered cyclic alkenyl ethers. The expected pyran derivatives **6h** and **6i** were obtained in excellent yields (entries 8 and 9, Table 3). Further extension showed that 7-membered cyclic ethers such as **6j** could also be achieved (entry 10, Table 3). This example clearly demonstrated the potential of the above method in the synthesis of natural products having the same bicyclic skeleton, such as Sarsolenone.[11]

Comparison of **3e**, **3i** and **3j** revealed that the formation of the 5-membered ring is faster than that of the 6-membered ring, which in turn is much faster than that of the 7-membered ring. A direct comparison can also be found in the reaction of dibromo-substituted substrate **3d**, which furnished the dihydrofuran product **6d** while no corresponding pyran derivative could be detected (entry 4, Table 1). This trend might be attributed to the steric requirement for the cyclization.

In conclusion, we have developed a simple protocol for the general and efficient synthesis of cyclic alkenyl ethers. The ease with which the procedure can be conducted and the mild experimental conditions should make this an important methodology in natural product synthesis.

This project was supported by the National Natural Science Foundation of China (Nos. 20325207 and 20472109) and by the Shanghai Municipal Committee of Science and Technology (No. 04QMH1418).

Notes and references

‡ Typical procedure for the copper-catalyzed cyclization of bromoenones **3**: CuI (3.8 mg, 0.02 mmol), bromoenone **3** (0.4 mmol) and K_2CO_3 (110 mg, 0.8 mmol) were added to a round flask under nitrogen, *N*,*N*′-Dimethylethylenediamine (4.3 μL, 0.04 mmol) and THF (4 mL) were then added under nitrogen. The mixture was stirred at refluxing temperature. After the reaction was complete, the resulting mixture was cooled down to r.t. and ethyl acetate (20 mL) was added. The mixture was then filtered and the filtrate was concentrated under reduced pressure. The crude product **6** was purified by column chromatography on silica gel with hexane-ethyl acetate in an appropriate ratio as the eluent.

1 For examples, see: (*a*) W. Birnecker, B. Wallnofer, O. Hoffer and H. Greger, *Tetrahedron*, 1988, **44**, 267; (*b*) J. A. Mareo, J. F. Sanz, J. Jakupovic and S. Huneck, *Tetrahedron*, 1990, **46**, 6931; (*c*) G. Wurz, O. Hofer, J. F. Sanz-Cervera and J. A. Marco, *Ann. Chem.*, 1993, 99; (*d*) W. Wang, T. Li, R. Milburn, J. Yates, E. Hinnant, M. J. Luzzio, S. A. Noble and G. Attardo, *Biorg. Med. Chem. Lett.*, 1998, **8**, 1579; (*e*) W. Wang, T. Breining, T. Li, R. Milburn and G. Attardo, *Tetrahedron Lett.*, 1998, **39**, 2459; (*f*) Y. Nakamura, N. Kawamoto, Y. Ohto, K. Torikai, A. Murakami and H. Ohigashi, *Cancer Lett.*, 1999, **140**, 37.

2 For examples, see: (*a*) T. Nicola, R. Vieser and W. Eberbach, *Eur. J. Org. Chem.*, 2000, 527; (*b*) K. Kobayashi, M. Uchida, T. Uneda, K. Yoneda, M. Tanmatsu, O. Morikawa and H. Konishi, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2977; (*c*) T. N. Van, B. Kesteleyn and N. D. Kimpe, *Tetrahedron*, 2001, **57**, 4213; (*d*) N. Asao, T. Nogami, K. Takahashi and Y. Yamamoto, *J. Am. Chem. Soc.*, 2002, **124**, 764; (*e*) J. Barluenga, H. Vazquez-Villa, A. Ballesteros and J. M. Gonzalez, *J. Am. Chem. Soc.*, 2003, **125**, 9028; (*f*) N. T. Patil and Y. Yamamoto, *J. Org. Chem.*, 2004, **69**, 5139.

3 For selected examples, see: (*a*) B. Gabriele and G. Salerno, *Chem. Commun.*, 1997, 1083; (*b*) B. Gabriele, G. Salerno and E. Lauria, *J. Org. Chem.*, 1999, **64**, 7687; (*c*) F. E. McDonald, K. S. Reddy and Y. Diaz, *J. Am. Chem. Soc.*, 2000, **122**, 4304; (*d*) W. W. Cutchins and F. E. McDonald, *Org. Lett.*, 2002, **4**, 749; (*e*) C. G. Bates, P. Saejueng, J. M. Murphy and D. Venkataraman, *Org. Lett.*, 2002, **4**, 4727; (*f*) B. M. Trost and Y. H. Rhee, *J. Am. Chem. Soc.*, 2002, **124**, 2528; (*g*) J. Zhu, A. R. Germain and J. A. Porco, Jr., *Angew. Chem., Int. Ed.*, 2004, **43**, 1239; (*h*) X. Han and R. A. Widenhoefer, *J. Org. Chem.*, 2004, **69**, 1738.

4 For reviews, see: (*a*) K. Kunz, U. Scholz and D. Ganzer, *Synlett*, 2003, 2428; (*b*) S. V. Ley and A. W. Thomas, *Angew. Chem. Int. Ed.*, 2003, **42**, 5400; (*c*) J. R. Dehli, J. Legros and C. Bolm, *Chem. Commun.*, 2005, 973.

5 For the latest examples, see: (*a*) A. Klapars, S. Parris, K. W. Anderson and S. L. Buchwald, *J. Am. Chem. Soc.*, 2004, **126**, 3529; (*b*) J. C. Antilla, J. M. Baskin, T. E. Barder and S. L. Buchwald, *J. Org. Chem.*, 2004, **69**, 5578; (*c*) S. U. Son, I. K. Park and T. Hyeon, *Chem. Commun.*, 2004, 778; (*d*) H.-J. Cristau, P. P. Cellier, J.-F. Spimdler and M. Taillefer, *Eur. J. Org. Chem.*, 2004, 695; (*e*) R. Hosseinzadeh, M. Tajbakhsh, M. Mohadjerani and H. Mehdinejad, *Synlett*, 2004, 1517; (*f*) K.-Y. Kim, J.-T. Shim, K.-S. Lee and C.-G. Cho, *Tetrahedron Lett.*, 2004, **45**, 117; (*g*) M. V. Nandakumar, *Tetrahedron Lett.*, 2004, **45**, 1989; (*h*) W. Deng, Y.-F. Wang, Y. Zou, L. Liu and Q.-X. Guo, *Tetrahedron Lett.*, 2004, **45**, 4257; (*i*) N. Taniguchi and T. Onami, *J. Org. Chem.*, 2004, **69**, 915; (*j*) H.-J. Cristau, P. P. Cellier, J.-F. Spindler and M. Taillefer, *Chem. Eur. J.*, 2004, **10**, 5607; (*k*) G. F. Manbeck, A. J. Lipman, R. A. Stockland, Jr., A. L. Freidl, A. F. Hasler, J. J. Stone and I. A. Guzei, *J. Org. Chem.*, 2005, **70**, 244; (*l*) Z. Lu and R. J. Twieg, *Tetrahedron*, 2005, **61**, 903; (*m*) P.-S. Wang, C.-K. Liang and M.-k. Leung, *Tetrahedron*, 2005, **61**, 2931.

6 For reviews, see: (*a*) A. R. Muci and S. L. Buchwald, *Top. Curr. Chem.*, 2002, **219**, 131; (*b*) J. F. Hartwig, in *Handbook of Organopalladium Chemistry for Organic Synthesis*; E.-i. Negichi, Ed.; Wiley: New York, 2002; Vol. 1, p 1051; (*c*) A. F. Little and G. C. Fu, *Angew. Chem. Int. Ed.*, 2002, **41**, 4176; (*d*) D. Prim, J. M. Campagne, D. Joseph and B. Andrioletti, *Tetrahedron*, 2002, **58**, 2041; (*e*) B. Y. Yang and S. L. Buchwald, *J. Organomet. Chem.*, 1999, **576**, 125; (*f*) J. P. Wolfe, S. Wagaw, J. F. Marcoux and S. L. Buchwald, *Acc. Chem. Res.*, 1998, **31**, 805; (*g*) J. F. Hartwig, *Angew. Chem., Int. Ed.*, 1998, **37**, 2046; (*h*) J. F. Hartwig, *Acc. Chem. Res.*, 1998, **31**, 852.

7 (*a*) T. Ogawa, T. Kiji, K. Hayami and H. Suzuki, *Chem. Lett.*, 1991, 1443; (*b*) R. Shen and J. A. Porco, Jr., *Org. Lett.*, 2000, **2**, 1333; (*c*) R. Shen, C. T. Lin and J. A. Porco, Jr., *J. Am. Chem. Soc.*, 2002, **124**, 5650; (*d*) L. Jiang, G. E. Job, A. Klapars and S. L. Buchwald, *Org. Lett.*, 2003, **5**, 3667; (*e*) X. Wang and J. A. Porco, Jr., *J. Am. Chem. Soc.*, 2003, **125**, 6040; (*f*) C. Han, R. Shen, S. Su and J. A. Porco, Jr., *Org. Lett.*, 2004, **6**, 27; (*g*) R. S. Coleman and P.-H. Liu, *Org. Lett.*, 2004, **6**, 577; (*h*) X. Pan, Q. Cai and D. Ma, *Org. Lett.*, 2004, **6**, 1809.

8 (*a*) G. Nordmann and S. L. Buchwald, *J. Am. Chem. Soc.*, 2003, **125**, 4978; (*b*) Z. Wan, C. D. Jones, T. M. Koenig, Y. J. Pu and D. Mitchell, *Tetrahedron Lett.*, 2003, **44**, 8257; (*c*) M. Keegstra, *Tetrahedron*, 1992, **48**, 2681.

9 The reaction of 2,3-dibromo-1-propene with ethyl acetoacetate in DMSO with K_2CO_3 as the base was reported, which also afforded the product similar to **8**. See: (*a*) S. T. Akhmedov, N. S. Sadygov, V. M. Ismailov, M. A. Achundova, H. K. Sadovaya, F. N. Karimov and N. S. Zefirov, *Khim. Geterotsikl. Soedin.*, 1986, **12**, 1602; (*b*) S. T. Akhmedov, N. S. Sadygov, V. M. Ismailov, H. K. Sadovaya, F. N. Karimov and N. S. Zefirov, *Khim. Geterotsikl. Soedin.*, 1984, **10**, 1428; (*c*) For the mechanism of the rearrangement, also see A. S. Demir, I. M. Akhmedov and O. Sesenoglu, *Tetrahedron*, 2002, **58**, 9793.

10 T. Ogawa, K. Hayami, H. Iyama and H. Suzuki, *Chem. Lett.*, 1990, 937.

11 M. Zhang, K. Long, K. Ma, X. Huang and H. Wu, *J. Nat. Prod.*, 1995, **58**, 414.

