ORGANIC
LETTERS

2009
Vol. 11, No. 18
4084−4087

Synthesis of Enol Lactones via Cu(I)-Catalyzed Intramolecular O-Vinylation of Carboxylic Acids

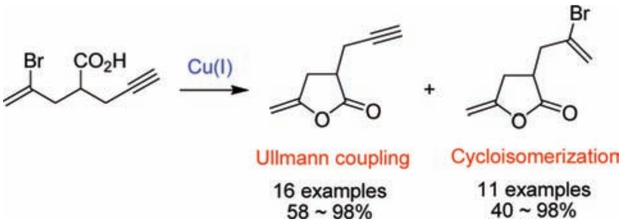
Changhui Sun,[†] Yewen Fang,[‡] Shuang Li,[†] Yue Zhang,[‡] Qiwu Zhao,[‡] Shana Zhu,[‡] and Chaozhong Li*,[†,‡]

*Department of Chemistry, Tongji University, 1239 Siping Road, Shanghai 200092,
P. R. China, and Key Laboratory of Synthetic Chemistry of Natural Substances,
Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences,
345 Lingling Road, Shanghai 200032, P. R. China*

clig@mail.sioc.ac.cn

Received July 9, 2009

ABSTRACT



With the catalysis of CuI/*trans-N,N′*-dimethylcyclohexane-1,2-diamine, a number of carboxylic acids underwent efficient intramolecular O-vinylation with vinyl bromides leading to the synthesis of the corresponding five- and six-membered enol lactones. The same catalytic system also led to the efficient cycloisomerization of alkynoic acids.

Enol lactones are structural motifs in many biologically active natural products such as cyanobacterin[1] and eresmofarfugin A.[2] They are also versatile intermediates in organic synthesis. The preparations of enol lactones have long been an important target and continue to be actively pursued. Conventional methods typically involve the halolactonization of alkynoic acids[3] or the halolactonization of alkenoic acids followed by dehydrohalogenation.[4] Recent progress has been made in the cycloisomerization of alkynoic acids, providing an atom-economic entry to enol lactones.[5] A number of transition metal complexes have been shown to catalyze these transformations with variable degrees of regio- and stereoselectivity.[6] It could be envisioned that transition-metal-catalyzed intramolecular cross-coupling reactions between carboxylic acids and alkenyl halides would allow the direct and stereospecific synthesis of enol lactones. However, this strategy remains virtually unexplored. Herein we report that the copper-catalyzed intramolecular O-vinylation of car-

---

[†] Tongji University.

[‡] Chinese Academy of Sciences.

(1) Mason, C. P.; Edwards, K. R.; Carlson, R. E.; Pignatello, J.; Gleason, F. K.; Wood, J. M. *Science* **1982**, *215*, 400.

(2) Tori, M.; Shiotani, Y.; Tanaka, M.; Nakashima, K.; Sono, M. *Tetrahedron Lett.* **2000**, *41*, 1797.

(3) (a) Sofia, M. J.; Chakravarty, P. K.; Katzenellenbogen, J. A. *J. Org. Chem.* **1983**, *48*, 3318. (b) Krafft, G. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 5459.

(4) For an example, see: Maddess, M. L.; Lautens, M. *Synthesis* **2004**, 1399.

(5) For reviews, see: (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (b) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (c) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368.

(6) For recent selected examples, see: (a) Mindt, T. L.; Schibli, R. *J. Org. Chem.* **2007**, *72*, 10247. (b) Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genet, J.-P.; Michelet, V. *J. Am. Chem. Soc.* **2006**, *128*, 3112. (c) Harkat, H.; Weibel, J.-M.; Pale, P. *Tetrahedron Lett.* **2006**, *47*, 6273. (d) Imagawa, H.; Fujikawa, Y.; Tsuchihiro, A.; Kinoshita, A.; Yoshinaga, T.; Takao, H.; Nishizawa, M. *Synlett* **2006**, 639. (e) Takei, I.; Wakebe, Y.; Suzuki, K.; Enta, Y.; Suzuki, T.; Mizobe, Y.; Hidai, M. *Organometallics* **2003**, *22*, 4639. (f) Jimenez-Tenorio, M.; Puerta, M. C.; Valerga, P.; Moreno-Dorado, F. J.; Guerra, F. M.; Massanet, G. M. *Chem. Commun.* **2001**, 2324.

10.1021/ol9015578 CCC: $40.75

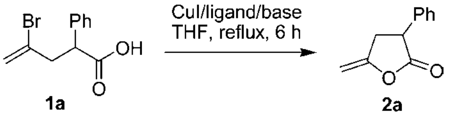
boxylic acids with alkenyl bromides provides an efficient and general route to the synthesis of enol lactones.

The past few years have witnessed a rapid progress in the formation of aryl (or vinyl) C−X bonds (X = N, O, S, etc.) via copper-catalyzed Ullmann coupling between aryl (or vinyl) halides and heteroatom-centered nucleophiles.[7] The high stability and low costs of the copper catalysts make these transformations attractive for industrial applications. By the appropriate choice of copper source, ligand, base, and solvent, these reactions have been developed to include a wide range of substrates under mild conditions. Various O-centered nucleophiles such as alcohols and ketone enolates can be successfully used for the coupling reactions. However, the use of carboxylates as the nucleophiles remains far less explored.[8] Thasana and co-workers recently reported the preparation of benzopyranones via the cyclization of 2′-halobiaryl-2-carboxylic acids under microwave irradiation using stoichiometric amounts of Cu(I).[8a] Their method failed to provide simpler lactones starting from nonaromatic carboxylic acids; only decarboxylation was observed. Driven by our interest in Cu(I)-catalyzed intramolecular vinlyation reactions,[9] we set out to study the intramolecular O-vinylation of carboxylic acids.

Thus, 4-bromo-2-phenylpent-4-enoic acid (**1a**) was chosen as the model substrate. Compound **1a** was first subjected to the following typical Ullmann coupling conditions: CuI (10 mol %), 1,10-phenanthroline (Phen, 20 mol %),[10] K_2CO_3 (2 equiv) in refluxing THF. No reaction occurred within 6 h (entry 1, Table 1). Switching the ligand to L-proline[11] did not help. To our delight, when *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA)[12] was used as the ligand, the expected product **2a** was obtained in 25% yield (entry 3, Table 1). The best result (87% yield of **2a**) was achieved with *N*,*N*′-dimethylcyclohexane-1,2-diamine[13] (DMCHDA) as the ligand (entry 5, Table 1). Lowering the amounts of CuI and DMCHDA resulted in a slight decrease of the yield of **2a** (entry 9, Table 1). We next examined the effects of different bases. It turned out that K_2CO_3 was superior to Cs_2CO_3, K_3PO_4, and Na_2CO_3 (entries 5−8, Table 1). As a comparison, the coupling did not proceed at all without either CuI or the ligand or the base (entries 10−12, Table 1).

With the optimized combination (entry 5, Table 1) in hand, we then examined the generality of this method (Table 2). Substrates **1a**−**1f** bearing different substituents at the C-2 position all afforded the expected cyclization products in high yields (entries 1−6, Table 2). Dialkyl substitution at the C-2

Table 1. Optimization of the Synthesis of **2a** from **1a**

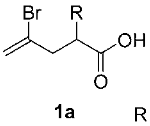
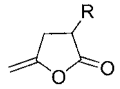
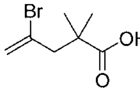
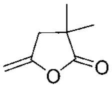
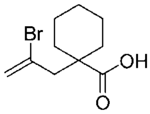
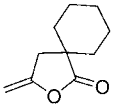
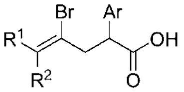
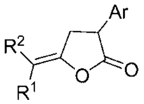
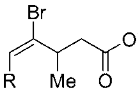
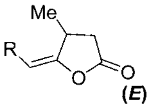
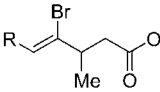
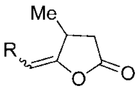


1a **2a**

entry[a]	ligand (mol %)[b]	base	yield (%)[c]
1	Phen (20)	K_2CO_3	0
2	L-proline (20)	K_2CO_3	0
3	TMEDA (20)	K_2CO_3	25
4	DMEDA (20)	K_2CO_3	76
5	**DMCHDA (20)**	**K_2CO_3**	**87**
6	DMCHDA (20)	K_3PO_4	60
7	DMCHDA (20)	Cs_2CO_3	27
8	DMCHDA (20)	Na_2CO_3	0
9[d]	DMCHDA (10)	K_2CO_3	76
10	none	K_3PO_4	0
11	DMCHDA (20)	none	0
12[e]	DMCHDA (20)	K_2CO_3	0

[a] Reaction conditions: **1a** (0.3 mmol), CuI (0.03 mmol), ligand (0.06 mmol), base (0.6 mmol), THF (3 mL), reflux, 6 h. [b] Phen: 1,10-phenanthroline. TMEDA: *N*,*N*,*N*′,*N*′-tetramethylethylenediamine. DMEDA: *N*,*N*′-dimethylethylenediamine. DMCHDA: *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine. [c] Isolated yield based on **1a**. [d] 5 mol % of CuI was used. [e] No CuI was used.

Table 2. O-Vinylation of Carboxylic Acids **1**

entry[a]	substrate		product	time	yield (%)[b]
					
1	**1a**	R = Ph	**2a**	6 h	87
2	**1b**	R = *p*-$MeOC_6H_4$	**2b**	3 h	88
3	**1c**	R = Bn	**2c**	3 h	76
4	**1d**	R = C_8H_{17}	**2d**	7 h	74
5	 **1e**		 **2e**	15 min	85
6	 **1f**		 **2f**	30 min	95
					
7[c]	**1g**	R^1 = H, R^2 = Me	**2g**	30 min[d]	98
8[c]	**1h**	R^1 = R^2 = Me	**2h**	30 min[d]	95
9[e]	 **1i**		 **(*E*)-2i**	6 h	86
10[e]	 **1j**		 **2i**	7 h	83[f]

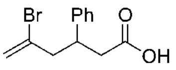
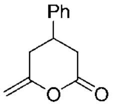
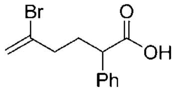
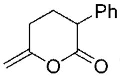
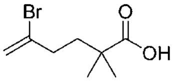
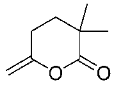
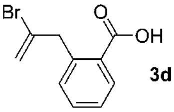
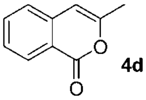
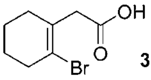
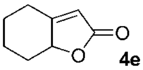
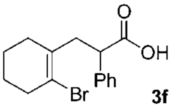
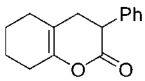
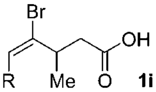
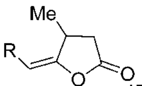
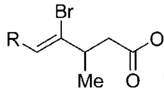
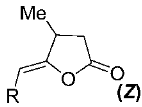
[a] Reaction conditions: **1** (0.3 mmol), CuI (0.03 mmol), DMCHDA (0.06 mmol), K_2CO_3 (0.6 mmol), THF (3 mL), reflux. [b] Isolated yield based on **1**. [c] The reaction was conducted in refluxing acetonitrile. [d] Ar = *p*-$MeOC_6H_4$. [e] R = *n*-$C_{10}H_{21}$. [f] *Z*:*E* = 83:17 determined by ^1H NMR (300 MHz).

---

(7) For reviews, see:(a) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (c) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (d) Deng, W.; Liu, L.; Guo, Q.-X. *Chin. J. Org. Chem.* **2004**, *24*, 150. (e) Dehli, J. R.; Legros, J.; Bolm, C. *Chem. Commun.* **2005**, 973. (f) Chemler, S. R.; Fuller, P. H. *Chem. Soc. Rev.* **2007**, *36*, 1153. (g) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (h) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450. (i) Evano, G.; Toumi, M.; Coste, A. *Chem. Commun.* **2009**, 4166.

(8) (a) Thasana, N.; Worayuthakarn, R.; Kradanrat, P.; Hohn, E.; Young, L.; Ruchirawat, S. *J. Org. Chem.* **2007**, *72*, 9379. (b) Yamamoto, T.; Kurata, Y. *Can. J. Chem.* **1983**, *61*, 86. (c) Yamamoto, T. *Synth. Commun.* **1979**, *9*, 219.

Table 3. Copper-Catalyzed Cyclization of Bromoenoic Acids

entry[a]	substrate	product	time	yield (%)[b]
1	 **3a**	 **4a**	2 h	84
2	 **3b**	 **4b**	2 h	73
3	 **3c**	 **4c**	2 h	77
4	 **3d**	 **4d**	2 h	71
5	 **3e**	 **4e**	4 h	58
6	 **3f**	 **4f**	2 h	64
7[c]	 **1i**	 **(*E*)-2i**	3 h	80
8[c]	 **1j**	 **(*Z*)-2i**	5 h	75

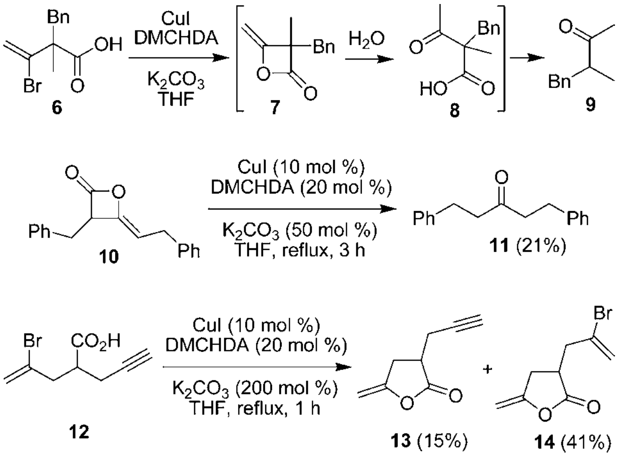
[a] Reaction conditions: **3** or **1** (0.3 mmol), CuI (0.03 mmol), DMCHDA (0.06 mmol), K_2CO_3 (0.15 mmol), CH_3CN (3 mL), reflux. [b] Isolated yield based on **3** or **1**. [c] R = *n*-$C_{10}H_{21}$.

position speeded up the coupling presumably because of the Thorpe−Ingold effect (entries 5 and 6, Table 2). Substrates **1g**−**1j** having an internal C═C bond also underwent smooth coupling reactions (entries 7−10, Table 2). The configuration of the C═C double bond was nicely retained in the cases of **1g** and **1i**, while partial isomerization occurred for the reaction of **1j** in a (*Z*)-configuration (entry 10, Table 2).

The above cross-coupling dealt with the cyclization in a 5-*exo*-like mode. We then extended this method to the coupling via a six-membered ring closure. Surprisingly, the model compound 5-bromo-3-phenylhex-5-enoic acid (**3a**) failed to give the cyclization product δ-lactone **4a** under the optimized conditions, while **3a** gradually decomposed. With the assumption that bromide **3a** might not be reactive enough, 5-iodo-3-phenylhex-5-enoic acid (**5**) as the iodo-analogue of **3a** was prepared and subjected to the above conditions. However, no expected product could be observed either. This led us to think that the true reason might be the instability of product **4a** under the reaction conditions. Thus, the amount of the base K_2CO_3 was reduced to 50 mol % to make the reaction solution less basic. Indeed, such a modification allowed the isolation of δ-lactone **4a** in 84% yield from the reaction of bromide **3a** in refluxing acetonitrile. The reoptimized conditions (10 mol % CuI, 20 mol % DMCHDA, 50 mol % K_2CO_3, CH_3CN, reflux) were then applied to the reactions of a variety of carboxylic acids, and the results are summarized in Table 3. 5-Bromohex-5-enoic acids **3a**−**3c** afforded the corresponding *exo*-lactones **4a**−**4c** in high yields. Aromatic carboxylic acid **3d** also underwent smooth cyclization to furnish the isochromanone **4d**. The cross-coupling in a 5-*endo*-like mode was also successful as exemplified by the reaction of **3e** from which furanone **4e** was obtained as the isomerized product. The 6-*endo*-like cyclization (**3f**) was also implemented in a good efficiency. More importantly, the reoptimized conditions now allowed the retention of configuration of the C═C bond as evidenced by the reactions of **1i** and **1j** (entries 7 and 8, Table 3).

The results in Tables 2 and 3 prompted us to investigate the O-vinylation via a four-membered ring closure. Such a mode of cyclization was found by us to be fundamentally preferred over other modes of cyclization in Cu(I)-catalyzed intramolecular O-,[9d] N-,[9f] S-,[9i] and C-vinylation[9g] reactions. Therefore, substrates such as bromide **6** were subjected to the same treatment as above. To our disappointment, no expected products such as **7** could be obtained. Only ketones such as **9** were isolated in low yields (~20%). A plausible explanation was that the cyclization of **6** indeed took place to give the β-lactone **7**, which then underwent ring opening to generate the β-keto acid **8**. Further decarboxylation of **8** led to the formation of **9** (Scheme 1). The easy decarboxy-

Scheme 1



---

(9) (a) Fang, Y.; Li, C. *Chem. Commun.* **2005**, 3574. (b) Hu, T.; Li, C. *Org. Lett.* **2005**, *7*, 2035. (c) Lu, H.; Li, C. *Org. Lett.* **2006**, *8*, 5365. (d) Fang, Y.; Li, C. *J. Am. Chem. Soc.* **2007**, *129*, 8092. (e) Pan, Y.; Lu, H.; Fang, Y.; Fang, X.; Chen, L.; Qian, J.; Wang, J.; Li, C. *Synthesis* **2007**, 1242. (f) Zhao, Q.; Li, C. *Org. Lett.* **2008**, *10*, 4037. (g) Chen, L.; Shi, M.; Li, C. *Org. Lett.* **2008**, *10*, 5285. (h) Lu, H.; Yuan, X.; Zhu, S.; Sun, C.; Li, C. *J. Org. Chem.* **2008**, *73*, 8665. (i) Zhao, Q.; Li, L.; Fang, Y.; Sun, D.; Li, C. *J. Org. Chem.* **2009**, *74*, 459.

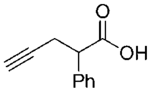
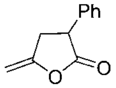
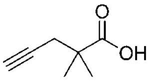
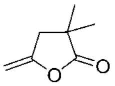
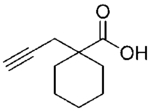
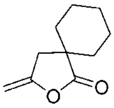
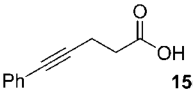
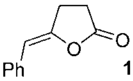
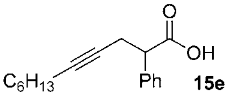
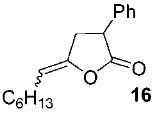
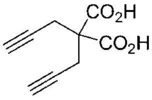
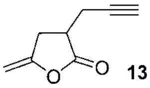
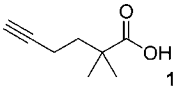
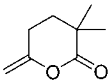
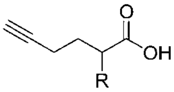
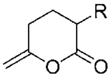
(10) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803.

(11) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453.

(12) Collman, J. P.; Zhong, M.; Zhang, C.; Costanzo, S. *J. Org. Chem.* **2001**, *66*, 7892.

(13) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684.

Table 4. Cycloisomerization of Alkynoic Acids **15**

entry[a]	substrate	product	time	yield (%)[b]
1	 **15a**	 **2a**	30 min	88
2	 **15b**	 **2e**	10 min	96
3	 **15c**	 **2f**	10 min	90
4[c]	 **15d**	 **16d**	6 h	80
5[c]	 **15e**	 **16e**[d]	6 h	69
6	 **15f**	 **13**	20 min	90
7	 **15g**	 **4c**	30 min	88
				
8	**15h** R = C_4H_9	**16h**	4 h	96
9	**15i** R = $Me_2C{=}CHCH_2$	**16i**	4 h	98
10	**15j** R = Ph	**4b**	20 h	40

[a] Reaction conditions: **15** (0.3 mmol), CuI (0.03 mmol), DMCHDA (0.06 mmol), K_2CO_3 (0.03 mmol), THF (3 mL), reflux. [b] Isolated yield based on **15**. [c] The reaction was conducted in refluxing acetonitrile. [d] *Z*:*E* = 7:1 determined by ^1H NMR (300 MHz).

lation of *β*-keto acids under Ullmann coupling conditions was previously observed by us.[14] To provide more evidence on this analysis, the diketene **10** was prepared according to the literature procedure[15] and treated under the above conditions. Within 3 h, all the diketene decomposed, and the ketone **11** was obtained in 21% yield. The similar outcome of the reactions of **10** and **6** strongly suggests that the O-vinylation of carboxylic acids via a four-membered ring closure is in fact an efficient process.

During our investigation on the functional group tolerance of the above O-vinylation processes, we found that the copper-catalyzed reaction of carboxylic acid **12** gave not only the expected coupling product **13** but also the cycloisomerization product **14**, the latter being the major product (Scheme 1). When a catalytic amount (10 mol %) of K_2CO_3 was used, product **14** was obtained in 70% yield, while only a trace amount of **13** could be detected. The formation of **14** indicated that the same catalyst system could be utilized for the cycloisomerization of alkynoic acids. Therefore, a number of alkynoic acids were subjected to the aforementioned experimental conditions without further optimization, and the results are summarized in Table 4. *Exo*-lactones were achieved in all cases. For internal alkynes, the (*Z*)-stereoselectivity was observed (entries 4 and 5, Table 4). The reaction of malonic acid **15f** afforded the monocycloisomerization product **13** in 90% yield (entry 6, Table 4). Apparently, the copper-catalyzed decarboxylation occurred prior to cyclization. The cyclization of hex-5-ynoic acids was also successfully implemented (entries 7−10, Table 4). It should be noted that Mindt and Schibli recently reported the first examples of Cu(I)-catalyzed cycloisomerization of alkynoic acids in aqueous media.[6a] Our method serves as a useful complement especially for those substrates that are insoluble or poorly soluble in water.

In conclusion, we have successfully developed the first examples of Cu(I)-catalyzed intramolecular O-vinylation of carboxylic acids leading to the convenient and efficient synthesis of five- and six-membered enol lactones under mild conditions. The same catalyst system also allows the efficient cycloisomerization of alkynoic acids. This chemistry should be of useful application in organic synthesis.

Acknowledgment. This project was supported by the NSFC (Grant Nos. 20672136, 20702060, and 20832006) and by the STCSM (Grant No. 07XD14038).

Supporting Information Available: Experimental procedures for O-vinylation and cycloisomerization and characterizations of **1**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9015578

---

(14) Fang, Y.; Li, C. *J. Org. Chem.* **2006**, *71*, 6427.

(15) (a) Clemens, R. J. *Chem. Rev.* **1986**, *86*, 241. (b) Kato, T. *Acc. Chem. Res.* **1974**, *7*, 265.