

Copper/Iron-Cocatalyzed Highly Selective Tandem Reactions: Efficient Approaches to γ -Alkylidene Lactones

Si Li,^a Wei Jia,^a and Ning Jiao^{a,b,*}

^a State Key Laboratory of Natural and Biomimetic Drugs, Peking University, School of Pharmaceutical Sciences, Peking University, Xue Yuan Rd. 38, Beijing 100191, People's Republic of China
Fax: (+86)-010-8280-5297; e-mail: jiaoning@bjmu.edu.cn

^b State Key Laboratory of Organometallic Chemistry, Chinese Academy of Sciences, Shanghai 200032, People's Republic of China

Received: November 11, 2008; Revised: February 9, 2009; Published online: March 12, 2009

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.200800695>.

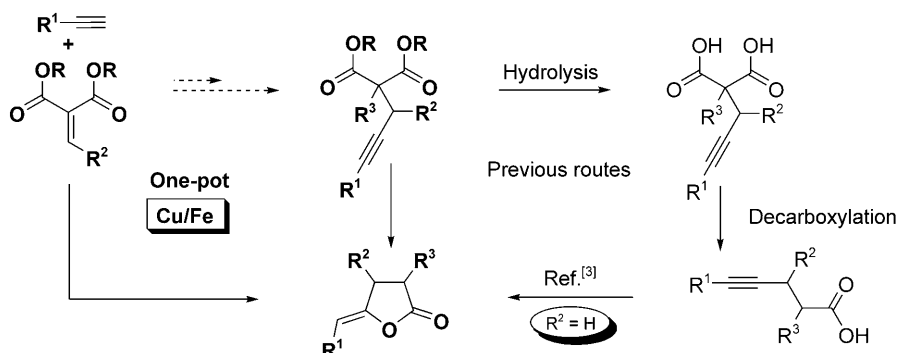
Abstract: Inexpensive copper/iron-cocatalyzed, efficient, highly regioselective and stereoselective one-pot tandem conjugate addition–cyclization–hydrolysis–decarboxylation reactions have been developed, which provide efficient tandem reactions for C–C and C–O bond formation, and the novel synthetic methods of γ -alkylidenebutylolactones.

Keywords: copper; cyclization; hydrolysis; iron; lactones

γ -Alkylidene lactones have attracted considerable attention due to their diverse biological activities and ubiquitous structural units in natural products,^[1,2] such as atranone^[2a] and growth regulating reagent.^[2b] In the past several decades, transition metal-catalyzed intramolecular hydroacyloxylation reactions of acetylenic acids have been demonstrated to construct this unique structural unit (Scheme 1).^[3] Among those previous studies, there remain several challenges to

be addressed: 1) The acetylenic acids as starting materials require several steps from their corresponding propargylmalonic esters^[4] *via* hydrolysis and decarboxylation generating waste from solvents and purifications (Scheme 1). 2) Generally, toxic and noble late transition metals such as Hg, Pd, Rh, Au, and Ag were employed.^[3] 3) 4-Substituted γ -alkylidenebutylolactones ($R^2 \neq H$, Scheme 1) could not be easily approached through the reported methods.^[5] Herein, we wish to report a novel and reliable method to construct substituted γ -alkylidenebutylolactones *via* inexpensive Cu/Fe cocatalysis starting from readily available aryl-substituted alkynes and 5-alkylidene-Meldrum's acids (Scheme 1) which can be easily precipitated in water *via* their relative condensation reactions.^[6]

Transition metal-catalyzed reactions have long been used for organic synthesis.^[7] Recently, the development of inexpensive, practical and environmentally benign catalytic system constitutes a challenging research area. In this concept, iron has been extensively investigated.^[8,9] Furthermore, inexpensive copper and iron-cocatalyzed reactions presented an attractive



Scheme 1. Synthesis of substituted γ -alkylidenebutylolactones *via* transition metal-catalyzed reactions.

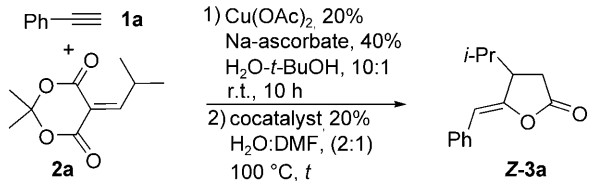
strategy in cooperative catalysis.^[10,11] However, copper and iron-cocatalyzed hydroacyloxylation of alkynes have never been documented. In the presented novel system, the first copper and iron-cocatalyzed highly selective tandem conjugate addition–cyclization–hydrolysis–decarboxylation reactions of alkynes and 5-alkylidene-Meldrum's acids were achieved leading to substituted *Z*- γ -alkylidenebutyrolactones, which represents one of the rare examples of efficient cooperative catalysis.

Our initial efforts focused on the metal-catalyzed tandem reaction of phenylacetylene **1a** with Meldrum's acid-derived Michael acceptors **2a**. Although the reactions of **1a** and **2a** catalyzed by metal catalysts, such as Au, Al, Ir, Cu and Fe in water gave **Z-3a** in low yields (Table S1, Supporting Information), FeCl₃ showed positive characteristics for the formation of **Z-3a** (Table S1, Supporting Information). We next examined the bimetallic catalysis: combining copper with iron catalysts in one step produced the expected product **Z-3a** in very low yield (7%) [Eq. (1)].

After further screening of different parameters, we were pleased to find that **Z-3a** was formed highly regioselectively and stereoselectively in 77% yield when the reaction was simply divided into two steps in one-pot (entry 2, Table 1). This one-pot operation is simple and practical. When the Cu(I)-catalyzed conjugate addition^[4b,12] as the first step was finished as monitored by TLC, FeCl₃ and DMF (1/2 volume of H₂O) were directly added, followed by heating at 100 °C for 55 min. However, only 12% of **Z-3a** was observed when the reaction was carried out in the absence of FeCl₃ (entry 1, Table 1). FeCl₃ was more effective than other iron catalysts, such as Fe(NO₃)₃ and Fe₂(SO₄)₃ (cf. entries 2–4, Table 1). It was noted that the yield decreased greatly to 24% when additional Cu(OAc)₂ (20 mol%) was added at the second step instead of FeCl₃ (entry 5). Lower yields were obtained by other metal cocatalysts (31–54%, entries 7–12). All the observed results indicate that the cooperative catalysis of copper and iron plays a key role for the high yield in these reactions. Lower yields were observed respectively when DMF was added in other ratios or in the absence of the additive (*t*-BuOH) (see Supporting Information). The structure of **Z-3a** was determined by X-ray diffraction (Figure 1).

Under these optimized one-pot conditions, aryl-substituted alkynes **1** reacted successfully with Mel-

Table 1. One-pot tandem conjugate addition–cyclization–hydrolysis–decarboxylation reaction of **1a** and **2a**.^[a]

			
Entry	Cocatalyst	<i>t</i> [min]	Yield of Z-3a [%]
1		40	12
2	FeCl ₃	55	77
3	Fe(NO ₃) ₃	60	41
4	Fe ₂ (SO ₄) ₃	50	55
5 ^[b]	Cu(OAc) ₂	120	24
6	Cu(OAc) ₂	120	30
7	PtCl ₂	65	40
8	AuCl ₃	65	36
9	IrCl ₃	70	31
10	MnO ₂	70	33
11	AgNO ₃	60	54
12	Pd(PhCN) ₂ Cl ₂	60	40

^[a] **1a** (1.0 mmol), **2a** (0.5 mmol), Cu(OAc)₂ (0.1 mmol), sodium ascorbate (0.2 mmol), and aqueous solvent (H₂O/*t*-BuOH = 10:1, 2.2 mL) were allowed to react at room temperature under N₂. Then 1 mL DMF and cocatalyst (0.1 mmol) were added to the reaction mixture and heated at 100 °C under air.

^[b] Sodium ascorbate (40%) was added.

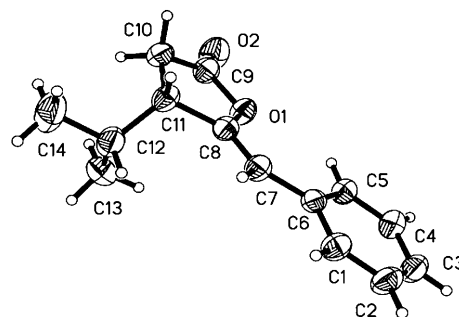


Figure 1. Crystal structure of **Z-3a**.

drum's acid-derived alkylidenes **2** containing alkyl, aryl and heteroaryl groups, leading to **Z-3** in moderate yields (Table 2, 37–77%). Since the **Z-3** products were produced from **1** and **2** via 4 steps (addition, cy-

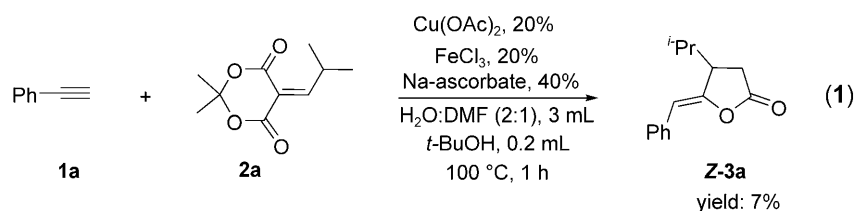
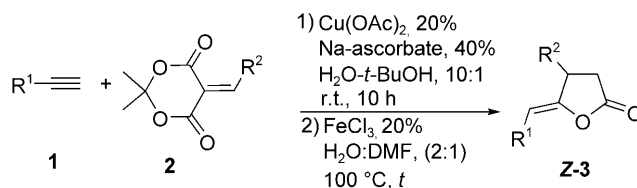


Table 2. One-pot tandem conjugate addition–cyclization–hydrolysis–decarboxylation reaction of **1** and **2**.^[a]

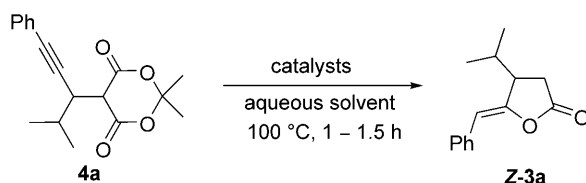
Entry	R ¹ (1)	R ² (2)	t [min]	Yield of Z-3 [%]
1	Ph (1a)	<i>i</i> -Pr (2a)	55	77 (Z-3a)
2	4-OMe-C ₆ H ₄ (1b)	<i>i</i> -Pr (2a)	30	66 (Z-3b)
3	3-Cl-C ₆ H ₄ (1c)	<i>i</i> -Pr (2a)	75	68 (Z-3c)
4	4-F-C ₆ H ₄ (1d)	<i>i</i> -Pr (2a)	45	57 (Z-3d)
5	4-Br-C ₆ H ₄ (1e)	<i>i</i> -Pr (2a)	60	48 (Z-3e)
6	2-F-4-F-C ₆ H ₄ (1f)	<i>i</i> -Pr (2a)	60	65 (Z-3f)
7	Ph (1a)	4-OMe-C ₆ H ₄ (2b)	60	51 (Z-3g)
8	Ph (1a)	Furan (2c)	70	37 (Z-3h)
9	Ph (1a)	4-Me-C ₆ H ₄ (2d)	60	53 (Z-3i)

^[a] **1** (1.0 mmol), **2** (0.5 mmol), $\text{Cu}(\text{OAc})_2$ (0.1 mmol), sodium ascorbate (0.2 mmol), and aqueous solvent ($\text{H}_2\text{O}/t$ -BuOH = 10:1, 2.2 mL) were allowed to react at room temperature under N_2 . Then 1 mL DMF and FeCl_3 (0.1 mmol) were added to the reaction mixture and heated at 100 °C under air.

clization hydrolysis, and decarboxylation), approximately >78% yield was achieved for each step.

These observed results inspired us to complete these Cu/Fe-cocatalyzed tandem methodologies. We then investigated the Cu/Fe-cocatalyzed tandem reactions of propargyl-Meldrum's acid **4** which can extend the substrate scope, such as with R³ groups (Table 4). Gratifyingly, **Z-3a** was highly regioselectively and stereoselectively formed in 81% yield cocatalyzed by $\text{Cu}(\text{OAc})_2$ and FeCl_3 under our optimized one-pot reaction conditions in 1 h (entry 3, Table 3). Further investigation indicated that the reaction achieved the highest yield (92%) when $\text{H}_2\text{O}/\text{DMF}$ (4:1) was used

as the aqueous solvent (entry 4, Table 3). As surmised, **Z-3a** was not observed when **4a** was treated under Cu(I)-catalyzed conjugate addition conditions even for 4 days (entry 1, Table 3). It is noteworthy that the yields were low (20% and 26%, respectively) when copper or iron was used alone, even when 40% Cu catalyst was used instead of a mixture of Cu (20 mol%) and Fe (20 mol%) (cf. entries 2 and 3, 4 and 6, Table 3). These results indicate that the presence of both copper and iron catalysts is essential for the high yield. The reactions did not work in the presence of base or acid (Table S3, Supporting Information).

Table 3. Transition metal-catalyzed decarboxylation–cyclization reaction of propargyl-Meldrum's acids **4a**.^[a]

Entry	Catalyst (%)	Cocatalyst (%)	Additive (%)	H_2O :DMF	Yield of Z-3a [%]
1 ^[b]	$\text{Cu}(\text{OAc})_2$ (20)		Na-ascorbate (40)	1:0	0
2	FeCl_3 (20)			2:1	26
3	$\text{Cu}(\text{OAc})_2$ (20)	FeCl_3 (20)	Na-ascorbate (40)	2:1	81
4	$\text{Cu}(\text{OAc})_2$ (20)	FeCl_3 (20)	Na-ascorbate (40)	4:1	92
5		FeCl_3 (20)	Na-ascorbate (40)	4:1	0 ^[c]
6	$\text{Cu}(\text{OAc})_2$ (40)		Na-ascorbate (80)	4:1	20 ^[d]

^[a] To **4a** (0.25 mmol) and catalyst, H_2O (1 mL) and DMF were added in the appropriate volume ratio and the mixture was allowed to react at 100 °C under air.

^[b] The reaction was carried out at room temperature for 4 days.

^[c] 80% of **4a** was recovered.

^[d] The reaction needed 8 h to finish completely.

Table 4. Cu/Fe-cocatalyzed decarboxylation–cyclization reaction of propargyl-Meldrum's acids **4**.^[a]

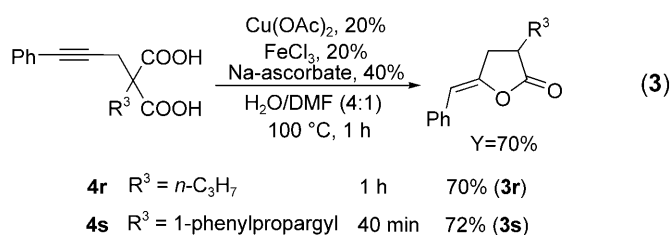
Entry	4	R ¹	R ²	R ³	Yield of Z-3 [%]
1	4a	Ph	<i>i</i> -Pr	H	92 (Z-3a)
2	4b	4-OMe-C ₆ H ₄	<i>i</i> -Pr	H	67 (Z-3b)
3	4c	3-Cl-C ₆ H ₄	<i>i</i> -Pr	H	69 (Z-3c)
4	4d	4-F-C ₆ H ₄	<i>i</i> -Pr	H	80 (Z-3d)
5	4e	4-Br-C ₆ H ₄	<i>i</i> -Pr	H	83 (Z-3e)
6	4f	2,4-di-F-C ₆ H ₃	<i>i</i> -Pr	H	68 (Z-3f)
7	4j	4-Me-C ₆ H ₄	<i>i</i> -Pr	H	68 (Z-3j)
8	4h	Ph	Furan	H	43 (Z-3h)
9	4i	Ph	4-Me-C ₆ H ₄	H	48 (Z-3i)
10	4k	Ph	Ph	H	51 (Z-3k)
11	4l	Ph	Et	H	46 (Z-3l)
12	4m	Ph	<i>c</i> -Hex	H	63 (Z-3m)
13	4n	Ph	<i>n</i> -Hex	H	52 (Z-3n)
14	4o	Ph	<i>i</i> -Bu	H	60 (Z-3o)
15	4p	Ph	<i>i</i> -Pr	Me	37 (Z-3p)

^[a] **1a** (0.25 mmol), Cu(OAc)₂ (0.05 mmol), FeCl₃ (0.05 mmol), sodium ascorbate (0.1 mmol), and aqueous solvent (H₂O/DMF = 4:1, 1.25 mL) were allowed to react at 100 °C under air.

The scope of this tandem cyclization–hydrolysis–decarboxylation reaction was expanded to a variety of substituted propargyl-Meldrum's acids (Table 4). These results show that the reaction is tolerant of a wide range of substituent groups on the propargyl-Meldrum's acids. Substrates with mostly aryl substituents at the R¹ position reacted efficiently (68–92%, see entries 1–7, Table 4). Particularly, the 4-bromoaryl-substituted product **Z-3e** (R¹ = 4-Br-C₆H₄) was obtained in 83% yield, which is amenable to further transformation (entry 5). In contrast with limited reports on 4-substituted γ -alkylidenebutylolactones, substrates bearing various demanding R² substituents, alkyl, aryl and heteroaryl groups, successfully afforded the expected 4-substituted γ -alkylidenebutylolactones with moderate yields under these conditions (entries 8–14, Table 4). Poly-substituted γ -alkylidene-

butyrolactone **Z-3p** can also be synthesized under these conditions with an acceptable yield (37%, entry 15, Table 4).

It is interesting to find that dipropargyl-Meldrum's acid **4q** did not afford the spiro-bis- γ -methylenebutyrolactone **5**, but gave a hydroxylation product **3q** in 39% yield. We were pleased to find that the yield increased to 62% when **4q'** was used as substrate [Eq. (2)]. The respective acids with different substitution at the R³ position, such as **4r** and **4s**, led to 3-substituted γ -alkylidenebutylolactones in good yields (70% and 72%, respectively) [Eq. (3)]. Therefore, γ -alkylidenebutylolactones with different R³ substituents can be successfully prepared under these conditions from the respective acids.



As we mentioned above, although acetylenic acids can be catalyzed by noble transition metal leading to corresponding lactones,^[3] β -substituted acetylenic acids, such as **6**, were rarely reported in these methods.^[5] It is of importance to note that acetylenic acid **6**, which was prepared from **4a** via hydrolysis and decarboxylation, successfully transformed to **Z-3a** in 68% yield under the optimized conditions (entry 1, Table 5). Compared with Cu/Fe cooperative catalysis, the yields decreased greatly when copper or iron was used as the sole catalyst (4% and trace, respectively) (*cf.* entries 1–3, Table 5).

Based on the above observed results, we have considered two pathways for the tandem reactions (Scheme 2). It is clear that the first conjugate addition step is catalyzed by Cu(I).^[4b,12] Although the collaboration of Cu and Fe was not clear yet, the compatibility of Cu and Fe is high. We believe that both of them act as Lewis acids to promote the cyclization. In the sense of hard-soft acid-base (HSAB) concept,^[13a] Fe(III) which is a harder Lewis acid than Cu(I) prefers to interact with the oxygen atom of the intermediate

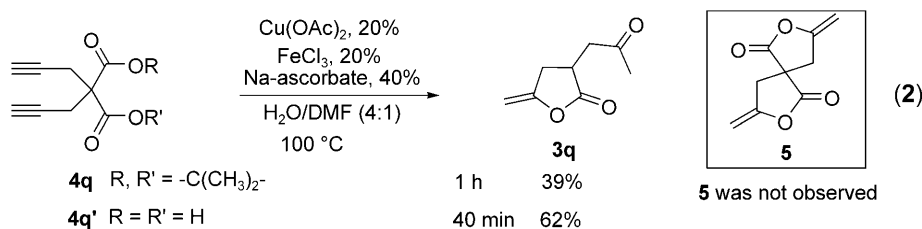
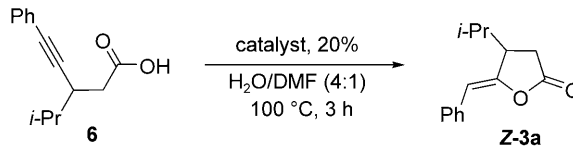
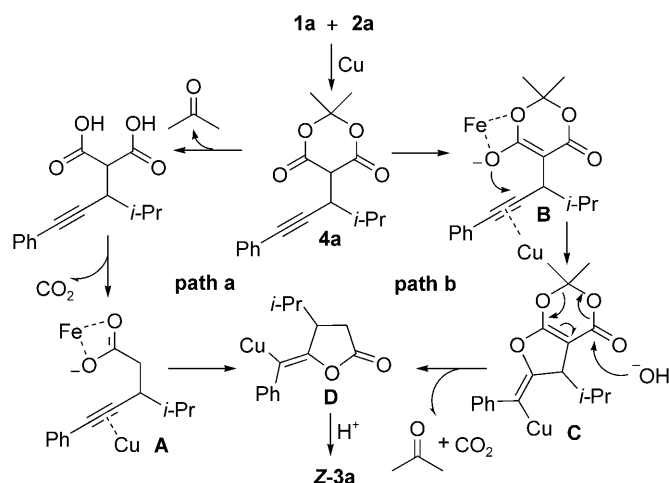


Table 5. Cu/Fe-cocatalyzed cyclization reaction of acetylenic acid **6**.


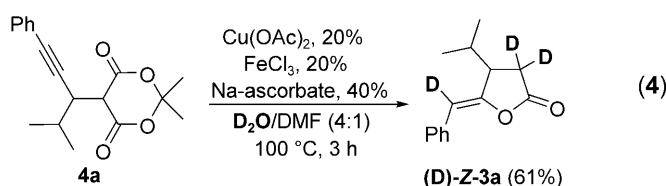
Entry	Catalyst	Cocatalyst	<i>t</i> [h]	Yield of Z-3a [%]
1	Cu(OAc) ₂ ^[a]	FeCl ₃	3	68
2	Cu(OAc) ₂ ^[a]		37	4
3		FeCl ₃	3	trace ^[b]
4	CuBr		24	8
5 ^[c]	CuBr		12	0 ^[d]

^[a] Sodium ascorbate (40% mol) was used.^[b] 78% of **6** was recovered.^[c] The reaction was carried at room temperature in the solvent (H₂O/*t*-BuOH = 1:1).^[d] 61% of **6** was recovered.**Scheme 2.** The proposed pathways for the tandem reaction.

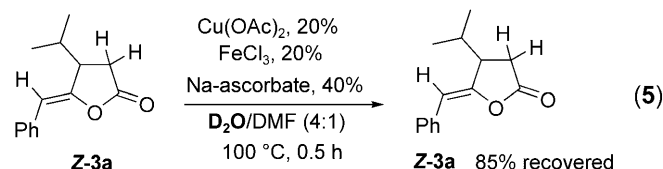
A or **B**.^[13,14] Simultaneously, Cu(I) binds and activates the π -system of the alkyne rendering it susceptible to be attacked by the O-nucleophile.^[13] In path **a**, intermediate **A** would be produced through hydrolysis and decarboxylation reactions, then the intramolecular hydroacyloxylation would proceed to give intermediate **D**. In path **b**, Fe as Lewis acid-promoted enolization of **3a** leads to intermediate **B**, which would undergo intramolecular cyclization giving intermediate **C**, followed by concurrent rearrangement^[15] and liberation of acetone and CO₂ to form intermediate **D**. A subsequent proton-transfer step from intermediate **D** affords the final product and regenerates metal catalysts. The high *Z* stereoselectivity can be explained reasonably on the *anti* intramolecular addition of the

intermediate **A** and **B** to the metal activated alkyne.^[3g,16]

The transformation from **4a** to **3a** has been tracked by HPLC. The product growth and substrate consumption were clear. However, acetylenic acid **6** was not observed during the process. On the other hand, compared to the 92% yield of the reaction using **4a** as substrate (entry 1, Table 4), the yield in cyclization of acetylenic acid **6** was very low (68%, entry 1, Table 5) under the same conditions. Moreover, the transformation from **6** took a much longer reaction time (3 h) than that from **4a** (1 h). To further understand this transformation, we carried out some preliminary mechanistic studies. Deuterated product [D]-**Z-3a** was isolated in 61% yield when D₂O was used instead of H₂O [Eq. (4)]. However, the hydrogen-deuterium ex-



change was not observed at the 5-position when **Z-3a** was treated with D₂O under the reaction conditions [Eq. (5)]. Based on these results, although both paths **a** and **b** are reasonable, we consider that the reactions prefer to occur through path **b**. A detailed mechanistic study is ongoing in our laboratory.



In conclusion, for the first time, we have developed Cu/Fe-cocatalyzed efficient and highly selective one-pot tandem reactions leading to poly-substituted γ -alkylidenebutyrolactones. This method has the following advantages: 1) the catalysts are cheap, less toxic and stable to air and moisture; 2) 4-substituted γ -alkylidenebutyrolactones can be successfully produced in this catalytic system; 3) the reactions are readily handled and carried out in aqueous solvent under air; 4) this method presents a rare example of efficient co-operative catalysis. The use of alkyl-substituted alkynes for the transformation remains a challenging task. Further studies on the reaction scope, mechanism and synthetic applications are ongoing in our laboratory.

Experimental Section

General Procedure A

A tube was charged with Cu(OAc)₂ (20 mg, 0.1 mmol), sodium ascorbate (40 mg, 0.2 mmol), and 2 mL H₂O, the mixture was stirred until the color turned orange. Subsequently, 102 mg of **1a** were added. The resulting mixture was stirring at room temperature for about 5 min, then 100 mg (0.5 mmol) of **2a** and 0.2 mL of *t*-BuOH were added. The reaction was stirred at room temperature under N₂ for 10 h as monitored by TLC. After the starting material had completely diminished, 1 mL of DMF and 16 mg (0.1 mmol) of FeCl₃ were subsequently added, then the reaction mixture was stirred at 100 °C for 55 min as monitored by TLC. Upon completion, the reaction was quenched with 10 mL saturated NH₄Cl solution and extracted three times with dichloromethane (10 mL each). The organic layers were combined, and dried with Na₂SO₄. After evaporation. The crude mixture was purified by silica gel chromatography (eluent: petroleum ether/ethyl acetate=20:1) to afford **Z-3a**; yield: 84 mg (77%).

General Procedure B

A mixture of Cu(OAc)₂ (10 mg, 0.05 mmol), sodium ascorbate (20 mg, 0.1 mmol), and 1 mL H₂O was stirred until the color turned orange, then **4a** (75 mg, 0.25 mmol), FeCl₃ (8 mg, 0.05 mmol), and DMF (0.25 mL) were added. The resulting mixture was stirred at 100 °C for 1 h as monitored by TLC. Work-up of the mixture was the same as for procedure A and afforded **Z-3a** as a solid; yield: 50 mg (92%); ¹H NMR (300 MHz, CDCl₃): δ=7.58 (d, *J*=1.2 Hz, 2H), 7.36–7.31 (m, 2H), 7.26–7.18 (m, 1H), 5.53 (s, 1H), 3.16–3.09 (m, 1H), 2.73 (dd, *J*=18.2, 9.9 Hz, 1H), 2.47 (dd, *J*=18.2, 3.9 Hz, 1H), 2.07–1.96 (m, 1H), 0.99 (d, *J*=6.8 Hz, 3H), 0.95 (d, *J*=6.8 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ=174.59, 151.65, 133.88, 128.41, 126.72, 105.38, 44.80, 31.94, 29.56, 19.54, 17.20; MS (70 eV): *m/z* (%)=216.3 (75 [M⁺], 118.2 (100).

Acknowledgements

Financial support from Peking University, National Science Foundation of China (Nos. 20702002, 20872003) and National Basic Research Program of China (973 Program 2009CB825300) are greatly appreciated.

References

- [1] a) D. M. Knight, *Contemp. Org. Synth.* **1994**, *1*, 287; b) E.-i. Negishi, M. Kitora, *Tetrahedron* **1997**, *53*, 6707–6738.
- [2] a) K. R. Edwards, *PCT Int. Appl.* **1982**, 19 pp; b) S. Huneck, K. Schreiber, *Phytochemistry*, **1972**, *11*, 2429–2434; c) S. F. Hinkley, J. A. Moore, J. Squillari, H. Tak, R. Oleszewski, E. P. Mazzola, B. B. Jarvis, *Magn. Reson. Chem.* **2003**, *41*, 337–343.
- [3] a) T. T. Jong, P. G. Willard, J. P. Porwoll, *J. Org. Chem.* **1984**, *49*, 735–736; b) G. A. Krafft, J. A. Katzenellenbogen, *J. Am. Chem. Soc.* **1981**, *103*, 5459–5466; c) N. Yanagihara, C. Lambert, K. Iritani, K. Utimoto, H. Nozaki, *J. Am. Chem. Soc.* **1986**, *108*, 2753–2754; d) D. M. T. Chan, T. B. Marder, D. Milstein, N. J. Taylor, *J. Am. Chem. Soc.* **1987**, *109*, 6385–6388; e) Z. Wang, X. Lu, *J. Org. Chem.* **1996**, *61*, 2254–2255; f) T. Wakabayashi, Y. Ishii, K. Ishikawa, M. Hidai, *Angew. Chem.* **1996**, *108*, 2268–2269; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2123–2124; g) E. Genin, P. Y. Toullec, S. Antonioti, C. Brancour, J.-P. Genêt, V. Michelet, *J. Am. Chem. Soc.* **2006**, *128*, 3112–3113; h) T. L. Mindt, R. Schibli, *J. Org. Chem.* **2007**, *72*, 10247–10250.
- [4] a) W. Skuballa, E. Schillinger, C. S. Stuerzebecher, H. Vorbrueggen, *J. Med. Chem.* **1986**, *29*, 313–315; b) T. F. Knöpfel, E. M. Carreira, *J. Am. Chem. Soc.* **2003**, *125*, 6054–6055; c) R. J. Brea, M. P. Lopez-Deber, L. Castedo, J. R. Granja, *J. Org. Chem.* **2006**, *71*, 7870–7873.
- [5] M. Cavicchioli, S. Decortiat, D. Bouyssi, J. Goré, G. Balme, *Tetrahedron* **1996**, *52*, 11463–11478.
- [6] F. Bigi, S. Carloni, L. Ferrari, R. Maggi, A. Mazzacani, G. Sartori, *Tetrahedron Lett.* **2001**, *42*, 5203–5205.
- [7] a) J. Tsuji, *Transition Metal Reagents and Catalysts*, John Wiley & Sons, New York, **2000**; b) M. Beller, C. Bolm, *Transition Metals for Organic Synthesis*, 2nd edn., John Wiley & Sons, New York, **2008**.
- [8] For leading reviews, see: a) C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217–6254; b) A. Fürstner, R. Martin, *Chem. Lett.* **2005**, *34*, 624–629; c) S. Enthaler, K. Junge, M. Beller, *Angew. Chem.* **2008**, *120*, 3363–3367; *Angew. Chem. Int. Ed.* **2008**, *47*, 3317–3321.
- [9] For some recent typical reports, see: a) M. S. Chen, M. C. White, *Science* **2007**, *318*, 783–787; b) Z. Lu, G. Chai, S. Ma, *J. Am. Chem. Soc.* **2007**, *129*, 14546–14547; c) M. P. Sibi, M. Hasegawa, *J. Am. Chem. Soc.* **2007**, *129*, 4124–4125; d) T. Hatakeyama, M. Nakamura, *J. Am. Chem. Soc.* **2007**, *129*, 9844–9845; e) A. Guérinot, S. Reymond, J. Cossy, *Angew. Chem.* **2007**, *119*, 6641–6644; *Angew. Chem. Int. Ed.* **2007**, *46*, 6521–6524; f) A. Correa, C. Bolm, *Angew. Chem.* **2007**, *119*, 9018–9021; *Angew. Chem. Int. Ed.* **2007**, *46*, 8862–8865; g) Z. Li, L. Cao, C.-J. Li, *Angew. Chem.* **2007**, *119*, 6625–6627; *Angew. Chem. Int. Ed.* **2007**, *46*, 6505–6507; h) M. Christmann, *Angew. Chem.* **2008**, *120*, 2780–2783; *Angew. Chem. Int. Ed.* **2008**, *47*, 2740–2742; i) A. Correa, M. Carril, C. Bolm, *Angew. Chem.* **2008**, *120*, 2922–2925; *Angew. Chem. Int. Ed.* **2008**, *47*, 2880–2883; j) B. Plietker, A. Dieskau, K. Mows, A. Jatsch, *Angew. Chem.* **2008**, *120*, 204–207; *Angew. Chem. Int. Ed.* **2008**, *47*, 198–201; k) J. Norinder, A. Matsumoto, N. Yoshikai, E. Nakamura, *J. Am. Chem. Soc.* **2008**, *130*, 5858–5859; l) Z. Li, R. Yu, H. Li, *Angew. Chem.* **2008**, *120*, 7607–7610; *Angew. Chem. Int. Ed.* **2008**, *47*, 7497–7500.
- [10] a) E. Shirakawa, T. Yamagami, T. Kimura, S. Yamaguchi, T. Hayashi, *J. Am. Chem. Soc.* **2005**, *127*, 17164–17165; b) M. Taillefer, N. Xia, A. Ouali, *Angew. Chem.* **2007**, *119*, 952–954; *Angew. Chem. Int. Ed.* **2007**, *46*, 934–936.
- [11] The Pd and Cu-cocatalyzed Sonogashira coupling reaction is one of the earliest and the most effective examples of bimetallic catalysis, see a) K. Sonogashira, Y.

- Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, 16, 4467–4470; for some reviews on cocatalysts see: b) E. K. van den Beuken, B. L. Feringa, *Tetrahedron* **1998**, 54, 12985–13011; c) E. Y.-X. Chen, T. J. Marks, *Chem. Rev.* **2000**, 100, 1391–1434; d) J. M. Lee, Y. Na, H. Han, S. Chang, *Chem. Soc. Rev.* **2004**, 33, 302–312; e) C. Wang, Z. Xi, *Chem. Soc. Rev.* **2007**, 35, 1395–1406.
- [12] a) T. F. Knöpfel, P. Zarotti, T. Ichikawa, E. M. Carreira *J. Am. Chem. Soc.* **2005**, 127, 9682–9683; b) S. Fujimori, E. M. Carreira, *Angew. Chem.* **2007**, 119, 5052–5055; *Angew. Chem. Int. Ed.* **2007**, 46, 4964–4967.
- [13] a) R. G. Pearson *J. Am. Chem. Soc.* **1963**, 85, 3533–3539; b) A. Corma, H. Garcia *Chem. Rev.* **2003**, 103, 4307–4365; c) N. T. Patil, Y. Yamamoto, *J. Org. Chem.* **2004**, 69, 5139–5142; d) C. Fehr, I. Farris, H. Sommer, *Org. Lett.* **2006**, 8, 1839–1841; e) P. O. Miranda, D. D. Diaz, J. I. Padron, M. A. Ramirez, V. S. Martin, *J. Org. Chem.* **2005**, 70, 57–62; f) R. Li, S. R. Wang, W. Lu, *Org. Lett.* **2007**, 9, 2219–2222.
- [14] a) N. V. Raghavan, D. L. Leussing, *J. Am. Chem. Soc.* **1976**, 98, 723–730; b) A. T. Khan, T. Parvin, L. H. Choudhury, *Tetrahedron* **2007**, 63, 5593–5601; c) K. Shuji, H. Masayuki, O. Fumiyasu, *Chem. Rec.* **2007**, 7, 137–149.
- [15] M. G. Organ, J. Wang, *J. Org. Chem.* **2002**, 67, 7847–7851.
- [16] H. Harkat, J.-M. Weibel, P. Pale, *Tetrahedron Lett.* **2006**, 47, 6273–6276.