

# Catalytic Enantioselective Alkylative Aldol Reaction: Efficient Multicomponent Assembly of Dialkylzincs, Allenic Esters, and Ketones toward Highly Functionalized $\delta$ -Lactones with Tetrasubstituted Chiral Centers

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**Abstract:** A general catalytic asymmetric alkylative aldol reaction is described as a new entry to the catalytic asymmetric multicomponent reaction (CAMCR). Highly functionalized  $\delta$ -lactones were produced in the presence of a catalytic amount of the Cu(OAc)<sub>2</sub>–DIFLUORPHOS complex through three-component assembly of dialkylzincs, allenic esters, and unactivated ketones. This CAMCR constructs two C–C bonds and one tetrasubstituted chiral center simultaneously. Conjugate addition of alkyl-copper species to an allenic ester produced highly active copper enolate in situ, and the successive asymmetric aldol addition to ketones followed by lactonization afforded the desired products. The addition of MS4A and Lewis base (Ph<sub>2</sub>S=O, DMSO, or HMPA) is important for obtaining a high yield, with suppression of the undesired  $\alpha$ -addition pathway. Control/crossover experiments suggest that the addition of a Lewis base facilitated the retro-aldol reaction of the  $\alpha$ -adducts (proofreading effect). The ketone and copper enolate generated through the retro-aldol reaction were converted to the desired lactone through the  $\gamma$ -aldol pathway, which was trapped by irreversible lactone formation.

# Introduction

The development of convergent, concise, functionalgroup-compatible, and stereoselective synthetic methodologies to produce novel carbon skeletons is in high demand. Such synthetic methodologies should rapidly produce densely functionalized small organic molecules from relatively simple reactants. These molecules constitute structurally distinct components for innovative medicinal/biochemical libraries with their diverse arrangement of multiple functional groups.<sup>1</sup>

Catalytic asymmetric multicomponent reactions (CAM-CRs),<sup>2,3</sup> which assemble three or more reagents together to stereoselectively form chiral molecules, would have a key role in such methodologies. Although CAMCR development is being actively studied and significant progress has been made,<sup>2</sup> an asymmetric construction of tetrasubstituted carbon centers by CAMCR is still in the early stages.<sup>4,5</sup> Such methodology could provide novel chiral building blocks not easily accessible using the currently existing methodologies. The development of such

reactions, however, is highly challenging for two main reasons. (1) The number of possible reaction pathways increases exponentially according to the number of reactants in a multicomponent reaction. (2) Substrates for chiral tetrasubstituted carbon synthesis (ketones and ketoimines) are relatively unreactive. Therefore, catalysts promoting such reactions should be highly active and precisely facilitate one specific desired reaction pathway out of the many side reaction pathways with excellent enantioselectivity.

Catalytic asymmetric aldol addition to ketones is one of the most attractive methodologies for constructing a functionalized skeletal backbone with a chiral tetrasubstituted center. Three groups, including ours,<sup>6</sup> have reported such reactions between unactivated ketones and silyl enolates. Although some of those

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<sup>(5)</sup> Reported CAMCR for the construction of a chiral tetrasubstituted carbon center: (a) Funabashi, K.; Ratni, H.; Kanai, M.; Shibasaki, M. J. Am. Chem. Soc. 2001, 123, 10784–10785. (b) Komanduri, V.; Krische, M. J. J. Am. Chem. Soc. 2006, 128, 16448–16449. See also ref 7b–d.

**Scheme 1.** Catalytic Reductive and Alkylative Aldol Reaction of Allenic Esters



reactions are highly stereoselective (enantio- and diastereoselective) and synthetically useful,<sup>6c,f</sup> *preactivation* of the nucleophiles is necessary.

In situ metal enolate generation via conjugate addition of a nucleophile to  $\alpha,\beta$ -unsaturated carbonyl compounds is an attractive alternative.<sup>2b</sup> In the case when a metal hydride (or its equivalent) is used as a nucleophile in the conjugate addition, a catalytic asymmetric *reductive* aldol reaction is realized (Scheme 1). Originating from the first intramolecular example by Lam,<sup>7a</sup> intermolecular catalytic asymmetric reductive aldol reactions to unactivated ketones were independently developed by Riant's group<sup>7b</sup> and our group<sup>7c,d</sup> using acrylate esters and allenic esters as the *pre*nucleophiles, respectively.

On the other hand, if organometallic reagents could be utilized as a trigger nucleophile, a catalytic asymmetric *alkylative* aldol reaction would be realized (Scheme 1).<sup>8</sup> There is a remarkable advantage of this type of reaction over the reductive variant, because further complex structures are accessible. Currently, however, catalytic asymmetric alkylative aldol reactions are restricted to enones as acceptors for the initial conjugate addition and aldehydes as acceptors for the subsequent aldol reaction. If more versatile  $\alpha$ , $\beta$ -unsaturated esters can be used as substrates

- (7) Čatalytic asymmetric reductive aldol reaction to unactivated ketones: (a) Lam, H. W.; Joensuu, P. M. Org. Lett. 2005, 7, 4225–4228. (b) Deschamp, J.; Chuzel, O.; Hannedouche, J.; Riant, O. Angew. Chem., Int. Ed. 2006, 45, 1292–1297. (c) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. Tetrahedron Lett. 2006, 47, 1403–1407. (d) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. J. Am. Chem. Soc. 2006, 128, 14440–14441.
- (8) Recent examples of catalytic asymmetric alkylative aldol reactions: (a) Yoshida, K.; Ogasawara, M.; Hayashi, T. J. Am. Chem. Soc. 2002, 124, 10984–10985. (b) Nicolaou, K. C.; Tang, W.; Dagneau, P.; Faraoni, R. Angew. Chem., Int. Ed. 2005, 44, 3874–3879. (c) Brown, M. K.; Degrado, S. J.; Hoveyda, A. H. Angew. Chem., Int. Ed. 2005, 44, 5306–5310. (d) Howell, G. P.; Fletcher, S. P.; Geurts, K.; ter Horst, B.; Feringa, B. L. J. Am. Chem. Soc. 2006, 128, 14977–14985 and references therein. See also ref 2b.
- (9) Several reports of catalytic enantioselecitve conjugate addition of organometallic reagents to α,β-unsaturated esters are present. Cu catalyst with Grignard reagents: (a) Kanai, M.; Tomioka, K. Tetrahedron Lett. 1995, 36, 4275–4278. (b) López, F.; Harutyunyan, S. R.; Minnaard, A. J.; Feringa, B. L. Angew. Chem., Int. Ed. 2005, 44, 2752–2756. (c) Harutynyan, S. R.; López, F.; Browne, W. R.; Correa, A.; Peña, D.; Badorrey, R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. J. Am. Chem. Soc. 2006, 128, 9103–9118. (d) López, F.; Minnaard, A. J.; Feringa, B. L. J. Am. Chem. Soc. 2007, 129, 276–277. Rh catalyst with arylboron reagents: (f) Xu, F.; Tillyer, R. D.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. Tetrahedron: Asymmetry 1998, 9, 1651–1655. (g) Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. Tetrahedron: Asymmetry 1999, 10, 4047–4056. (h) Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. J. Org. Chem. 2000, 65, 5951–5955. (i) Hayashi, T.; Yamasaki, K. Chem. Rev. 2003, 103, 2829–2844. (j) Navarre, L.; Pucheault, M.; Darses, S.; Genêt, J. -P. Tetrahedron Lett. 2005, 46, 4247–4250. (k) Paquin, J.-F.; Stephenson, C. R. J.; Defieber, C.; Carreira, E. M. Org. Lett. 2005, 7, 3821–3824.





 $^a$  Slowly added over 2 h.  $^b$  Determined by  $^1\text{H}$  NMR of the crude mixture on the basis of an internal standard method.  $^c$  Determined by chiral HPLC.  $^d$  A 1.6 equiv sample of Et<sub>2</sub>Zn was slowly added over 4 h.  $^e$  A 1.2 equiv sample of Et<sub>2</sub>Zn was slowly added over 1.5 h.  $^f$  (EtO)<sub>3</sub>SiF (20 mol % in entry 7 and 30 mol % in entry 8) was used as an additive.

in the first step (conjugate addition),<sup>9</sup> such CAMCRs should be synthetically more useful. Moreover, if ketones are used as substrates in the second aldol reaction, compounds containing chiral tetrasubstituted carbons can be constructed. The methodology involving above two, however, is not established.<sup>10,11</sup>

We report herein the first synthetically useful catalytic alkylative aldol reaction that assembles alkylzincs, allenic esters, and unactivated ketones to afford functionalized  $\delta$ -lactones with a tetrasubstituted chiral center. An interesting mechanistic insight with regard to the constitutional selectivity is also described.

#### **Results and Discussion**

To optimize the reaction conditions, we first selected acetophenone (1a), ethyl 2,3-butadienoate (2), and diethylzinc in hexane (3a) as substrates. At first, the CuOAc-DTBM-SEGPHOS catalyst, which afforded  $\gamma$ -adduct selectively in the previous reductive aldol protocol,7c,d was examined. Slow addition of 3a into a THF solution of 1a, 2, and the catalyst (5 mol %) produced the  $\gamma$ -adduct exclusively. The expected compound 5a was, however, isolated in only a tiny amount. The major product was lactone **4aa** (77% ee in 47% yield, Table 1, entry 1).<sup>12</sup> In constrast to the reductive aldol reaction, the addition of an achiral phosphine ligand, PCy<sub>3</sub>, significantly lowered the enantioselectivity (entry 2). By changing the chiral ligand to the sterically less demanding tol-BINAP, the reactivity was improved, and 4aa was obtained in 83% yield with 79% ee (entry 3). Extending the slow addition time to 4 h resulted in a decreased yield (entry 4). The use of divalent Cu(OAc)2 as a copper source slightly improved the enantioselectivity and

<sup>(6)</sup> Catalytic asymmetric aldol reaction to unactivated ketones: (a) Denmark, S. E.; Fan, Y. J. Am. Chem. Soc. 2002, 124, 4233-4235. (b) Denmark, S. E.; Fan, Y.; Eastgate, M. D. J. Org. Chem. 2005, 70, 5235-5248. (c) Moreau, X.; Tejeda, B.; Campagne, J. -M. J. Am. Chem. Soc. 2003, 125, 5644-5645. (e) Oisaki, K.; Stato, Y.; Kanai, M.; Shibasaki, M. J. Am. Chem. Soc. 2003, 125, 5644-5645. (e) Oisaki, K.; Zhao, D.; Suto, Y.; Kanai, M.; Shibasaki, M. Tetrahedron Lett. 2005, 46, 4325-4329. (f) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. J. Am. Chem. Soc. 2006, 128, 7164-7165. Recently, a copper-catalyzed asymmetric Mannich-type reaction to ketoimines was reported: (g) Suto, Y.; Kanai, M.; Shibasaki, M. J. Am. Chem. Soc. 2007, 129, 500-501.

<sup>(10)</sup> Very preliminary results (up to 88% ee and 60% yield, two examples) were reported in ref 7d.

Catalytic asymmetric *intramolecular* alkylative aldol reactions to unactivated ketones (two-component reactions) were reported. Rhodium catalysis: (a) Cauble, D. F.; Gipson, J. D.; Krische, M. J. J. Am. Chem. Soc. 2003, 125, 1110–1111. (b) Bocknack, B. M.; Wang, L. –C.; Krische, M. J. Proc. Natl. Acad. Sci. U.S.A. 2004, 101, 5421–5424. Copper catalysis: (c) Agapiou, K.; Cauble, D. F.; Krische, M. J. J. Am. Chem. Soc. 2004, 126, 4528–4529.

<sup>(12)</sup> The noncyclized products were obtained in the previous reductive aldol reaction (ref 7c,d). The difference is perhaps due to the higher nucleophilicity of zinc alkoxide than boron alkoxide.

Table 2. Optimization Using Aliphatic Ketone 1b



<sup>*a*</sup> Slowly added over 1.5 h. <sup>*b*</sup> Determined by <sup>1</sup>H NMR of the crude mixture on the basis of an internal standard method. <sup>*c*</sup> Determined by chiral HPLC. <sup>*d*</sup> Activated with a heat gun under reduced pressure (5 mmHg). The loading was 200 mg/mmol of **1b**. <sup>*e*</sup> Not determined. <sup>*f*</sup> Approximately 20% of **1b** remained.

yield (entry 5). Further screening of the chiral ligand led to the identification of DIFLUORPHOS<sup>13</sup> as the best ligand, producing 94% ee product at -20 °C (entry 6).

In the course of reaction optimization, a small amount of ketone 1a was always recovered. On the basis of the previous studies of the copper-catalyzed aldol reaction,<sup>6d,f</sup> we speculated that the ketone recovery was due to competitive enolization promoted by the highly basic intermediate copper alkoxide species (CuOEt or copper aldolate; see Scheme 3). In the previous case, the addition of (EtO)<sub>3</sub>SiF effectively shortened the lifetime of copper aldolate and enolization of ketones was sufficiently suppressed. Thus, we added a catalytic amount of (EtO)<sub>3</sub>SiF in the present system. As expected, recovery of ketone was significantly suppressed, and 4aa was produced in 95% vield with a minimum loss of enantioselectivity (entry 7). The loading of diethylzinc could be reduced to up to 1.2 equiv of ketone (entry 8). In this system, organometallic reagents other than dialkylzinc produced less satisfactory results; EtMgBr and Et<sub>3</sub>B resulted in no reaction, and Et<sub>3</sub>Al afforded inferior results on both conversion and enantioselectivity (20% yield, 23% ee under the conditions shown in entry 4).

When the above optimized conditions were applied to aliphatic ketone **1b**, however, lactone **4ba** was obtained in only 44% yield with concomitant production of a significant amount of  $\alpha$ -adducts **6** as a diastereomixture (Table 2, entry 1). To promote the desired  $\gamma$ -addition pathway, we screened the additives again. The addition of activated MS4A was promising (Table 2, entry 2): the yield of **4ba** increased to 64%, while the generation of **6** was decreased to ca. 10% yield. On the other hand, the addition of (EtO)<sub>3</sub>SiF accelerated the  $\alpha$ -adducts (the corresponding copper or zinc aldolates) were the kinetic products and (EtO)<sub>3</sub>SiF trapped the kinetic  $\alpha$ -aldolates. The  $\alpha$ -aldolates, however, would be labile if they were not trapped under the reaction conditions. We expected that it would be possible to

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	<b>`</b>	Ĭ		Cu(OAc) <sub>2</sub>	Cu(OAc) <sub>2</sub> (5 mol %)			
Ŭ +		OEt	+ R <sup>3</sup> <sub>2</sub> Zn (R)-I	-DIFLUORPHOS (6 mol %)			Pí ]	
R1	R <sup>2</sup>	u u	-	additive (	20 mol %)	F		₽3
1a	-h	" 2	3a-d	MS4A°, I	HF, –20°C		Ř²	IX.
		1.5 equiv	1.2 equiv <sup>a</sup>				4	
entry		product		additive	temp./ºC	time/h	yield/%° e	e/% <sup>d</sup>
1		0 L	4aa (X = H)	DMSO	-20	15	92	96 <sup>g</sup>
2	~		4ca (X = Br)	HMPA	-20	14	91	94
3	$\mathcal{O}$	Me	<sup>t</sup> 4da (X = OMe)	HMPA	-20	14	73	95
4	Ŷ		4ea	HMPA	-20	14	93	92
5	$\sim$		4ba	Ph <sub>2</sub> S=O	-20	14	95	87
6 <sup>e,f</sup>	$\bigcirc$		4fa	DMSO	-10	14	79	98
7 <sup>e,f</sup>	Me Me	o ↓ Me Q	4ga	DMSO	-10	15	76	96
8	$\bigcap$	o ↓ Me	4ha	DMSO	-20	42	67	94
9	$\sim$	0 II	4ab (R <sup>3</sup> = Me)	DMSO	-30	19+24	89	94
10	^	Ŷ.	4ac (R <sup>3</sup> = <sup>i</sup> Pr)	Ph <sub>2</sub> S=O	-20 <b>-≻</b> -10	10+12	78	84
11 <sup>e,f</sup>	$\bigcirc$	Me R	<sup>3</sup> 4ad (R <sup>3</sup> = <sup><i>n</i></sup> Bu)	Ph <sub>2</sub> S=O	-10	14	73	92
12 <sup>f</sup>		0 II	4bb (R <sup>3</sup> = Me)	DMSO	-20 <b>-≻</b> -10	17+24	61	86
13 <sup>e,f</sup>			4bc (R <sup>3</sup> = <sup>i</sup> Pr)	DMSO	0	48	50	78
14 <sup>e,f</sup>	$\sim$	Me R	<sup>3</sup> <b>4bd</b> (R <sup>3</sup> = <sup><i>n</i></sup> Bu)	Ph <sub>2</sub> S=O	-20	17+24	80	88

<sup>*a*</sup> Slowly added over 1.5 h. <sup>*b*</sup> Activated with a heat gun under reduced pressure (5 mmHg). The loading was 200 mg/mmol of **1**. <sup>*c*</sup> Isolated yield. <sup>*d*</sup> Determined by chiral HPLC analysis. <sup>*e*</sup> A 10 mol % concentration of the Cu source, 12 mol % ligand, and 1.6 equiv of dialkylzinc (slowly added over 1.5 h) were used. <sup>*f*</sup> CuTC was used instead of Cu(OAc)<sub>2</sub>. <sup>*g*</sup> The absolute configuration was determined to be *R*.

reconvert the kinetic  $\alpha$ -aldolates to the thermodynamically stable lactone **4ba** through an iterative retro-aldolization—aldolization process.<sup>14</sup>

On the basis of this assumption, we studied the effects of Lewis base additives that can facilitate the retro-aldol reaction by activating the metal–O bond of metal aldolate. As expected, the addition of diphenyl sulfoxide (Ph<sub>2</sub>S=O) suppressed the generation of  $\alpha$ -adducts (entry 4). TLC monitoring of the reaction profile suggested that Ph<sub>2</sub>S=O facilitated reconversion of the initially formed  $\alpha$ -adducts to the lactone through in situ destruction (i.e., retro-aldol reaction) of  $\alpha$ -products **6** (proof-reading effect). At the beginning of the reaction (after slow addition of Et<sub>2</sub>Zn, 1.5 h), a significant amount of  $\alpha$ -products **6** was observed in both the presence and the absence of Ph<sub>2</sub>S=O. The  $\alpha$ -products disappeared completely, however, after 12 h in the presence of Ph<sub>2</sub>S=O, and lactone **4ba** was slower

<sup>(13) (</sup>a) Jeulin, S.; de Paule, S. D.; Ratovelomanana-Vidal, V.; Genêt, J. -P.; Champion, N.; Dellis, P. Angew. Chem., Int. Ed. 2004, 43, 320–325. For other asymmetric catalyses in which DIFLUORPHOS works as an excellent chiral ligand, see: (b) Wadamoto, M.; Yamamoto, H. J. Am. Chem. Soc. 2005, 127, 14556–14557. (c) Sibi, M.; Tatamidani, H.; Patil, K. Org. Lett. 2005, 7, 2571–2573.

Table 3. Scope and Limitations

<sup>(14)</sup> In the case of aromatic ketone 1a (Table 1), α-adducts were observed in only trace amounts. A retro-aldol reaction of the α-aldolates derived from aromatic ketones might be faster than the silyl trap. Alternatively, the γ-adduct might be the kinetic product from aromatic ketones.



<sup>a</sup> The yield is determined by <sup>1</sup>H NMR of the crude mixture on the basis of an internal standard method.

Scheme 3. Proposed Catalytic Cycle



when the Lewis base additive was absent. In the absence of MS4A (entry 5), a significant amount (ca. 20%) of ketone **1b** was recovered. Therefore, the combined use of MS4A and Ph<sub>2</sub>S=O was essential to efficiently promote the desired  $\delta$ -lactone-forming pathway.<sup>15</sup>

Next, we investigated the scope and limitations of the reaction under the optimized conditions. We used different Lewis base additives depending on the substrates. In some cases (Table 3, entries 1–4, 9, and 12), DMSO or HMPA was favorable because isolation of lactone **4** from Ph<sub>2</sub>S=O was often problematic due to their very similar  $R_f$  values. In the case of entries 6–8 and 13, retroreaction of  $\alpha$ -adducts was sluggish at the indicated temperature in the presence of Ph<sub>2</sub>S=O. Thus, we selected a more Lewis basic additive (DMSO). In some cases, utilization of CuTC (copper thiophene-2-carboxylate)<sup>16</sup> as a stable Cu(I) source was favorable (entries 6, 7, and 11–14). Excellent enantioselectivity was generally obtained from both aromatic and aliphatic ketones with various dialkylzincs.<sup>17</sup>

To obtain insight into the reversibility from  $\alpha$ -products, we examined the following experiments using isolated  $\alpha$ -adducts **6** (0% ee). In the presence of a catalytic amount of CuTC– DIFLUORPHOS complex and Ph<sub>2</sub>S=O, **6** was treated with 1.2 equiv of diethylzinc at -20 °C (Scheme 2, eq 1). After 12 h,  $\alpha$ -adduct **6** completely disappeared and lactone **4ba** (65% yield, 88% ee) and noncyclized **5b** (12% yield) were produced. This

<sup>(15)</sup> MS4A might shorten the lifetime of copper alkoxides in the catalytic cycle by facilitating the alkoxide ligand exchange between Cu and Zn (from IV to I in Scheme 3), thus minimizing undesired reactions catalyzed by copper alkoxides (including enolization of the ketone). MS3A, MS5A, and MS13X showed similar effects.

<sup>(16)</sup> CuTC was prepared following the published procedure: Gallagher, W. P.; Maleczka, R. E., Jr. J. Org. Chem. 2003, 68, 6775-6779.
(17) (a) Propiophenone (14 h, 76% yield, 17% ee in the presence of HMPA)

<sup>(17) (</sup>a) Propiophenone (14 h, 76% yield, 17% ee in the presence of HMPA) and benzalacetone (16 h, 83% yield, 35% ee in the presence of HMPA) were unsatisfactory substrates. (b) At this stage, this catalytic system is not applicable to dialkenylzincs, diarylzincs, dialkynylzincs, or monoalky-lzinc halide (no reaction).

result clearly demonstrated that there is a retro-aldol reaction from  $\alpha$ -zinc aldolates (7 in Scheme 3) and the undesired  $\alpha$ -aldolates were converted to the stable and desired lactone (the proofreading effect). Interestingly, in the absence of a copper catalyst, the retro-aldol process barely proceeded, although Ph<sub>2</sub>S=O was present (eq 2), suggesting that involvement of the Cu catalyst is important for the proofreading effect. Next, a crossover experiment was conducted in the presence of acetophenone (1a) and 6 (eq 3). As a result, both 4aa and 4ba were obtained with high enantioselectivity via complete crossover. This result demonstrated that the retro-aldol reaction of 6 produced ketone 1b and vinylogous copper enolate in situ and an intermolecular recombination of ketone and copper enolate can proceed.

The probable catalytic cycle of the present reaction system is shown in Scheme 3. At first, Cu(II) is reduced to Cu(I) in the presence of alkylzinc to produce alkylcopper-phosphine complex I.18 Conjugate addition of alkylcopper I to allenic ester 2 affords copper enolate II, which is likely to be the actual active nucleophile of the following aldol reaction.<sup>19</sup> In the aldol reaction step, two kinds of copper aldolates  $\gamma$ -III and  $\alpha$ -III, could be produced.  $\alpha/\gamma$ -Selectivity seems to be highly dependent on the substrates and conditions.<sup>20</sup> Successive reaction of  $\alpha$ -III with dialkylzinc affords  $\alpha$ -zinc aldolate 7 and alkylcopper I. This  $\alpha$ -cycle is inherently reversible, and copper enolate II can be regenerated via a retro-aldol reaction from 7 (supported by the results shown in Scheme 2, eq 1). The Lewis base additive (sulfoxide and phosphoramide) facilitates this retroreaction by destabilizing  $\alpha$ -III with coordination to the zinc atom. On the other hand, from  $\gamma$ -III, successive lactonization produces the desired lactone 4 and copper ethoxide IV. In the absence of MS4A, regeneration of active species I might be slow. As a result, Brönsted base-promoted side reactions (such as enolization of ketones) could proceed. The  $\gamma$ -cycle involves an irreversible lactonization step and the intersection with the reversible  $\alpha$ -cycle with the copper enolate **II**. Consequently, all copper enolate **II** is consumed to convert ketones **1** to lactone **4** in the whole process.

## Conclusions

We report herein the development of a Cu–DIFLUORPHOS complex-catalyzed asymmetric alkylative aldol reaction producing highly functionalized chiral  $\delta$ -lactones via a three-component assembly of ketones, allenic esters, and alkylzincs. The reaction can be applied to a wide range of substrates. The addition of a Lewis base additive (Ph<sub>2</sub>S=O, DMSO, and HMPA) and MS4A was essential for the high product yield. Mechanistic studies suggest that the Lewis base additive accelerated the retro-aldol reaction of the undesired  $\alpha$ -product (proofreading effect). This new CAMCR entry for the construction of a chiral tetrasubstituted center will be useful for a convergent, concise, and diversity-oriented approach toward the development of innovative medicinal/biochemical libraries.

### **Experimental Section**

Typical Procedure for Catalytic Alkylative Aldol Reaction to Ketones. A catalyst solution was generated from Cu(OAc)2 (0.01 mmol, 5.0 mol %), (R)-DIFLUORPHOS (0.012 mmol, 6.0 mol %), a Lewis base additive (0.04 mmol, 20 mol %), and activated MS4A (40 mg, 200 mg/mmol of 1) in THF (0.25 mL) under stirring at room temperature for 10 min. Ethyl 2,3-butadienoate (2; 0.3 mmol, 1.5 equiv) and ketone 1 (0.2 mmol) were then added successively to the catalyst solution. After 10 min, dialkylzinc solution 3 (0.24 mmol, 1.2 equiv) was added slowly to the reaction mixture via a syringe pump for 1.5 h at -20 °C. The mixture was allowed to stir for the indicated time. MeOH was added to quench the reaction, and then the generated precipitate was filtered over a Celite pad. After evaporation of the solvent, the NMR yield was determined by <sup>1</sup>H NMR analysis of the crude product with 1,1,2,2-tetrachloroethane as the internal standard. Purification by silica gel column chromatography (eluent AcOEt/ hexane) gave the analytically pure lactone 4. The enantiomeric excess was determined by chiral HPLC analysis with 220 nm UV.

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**Supporting Information Available:** Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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<sup>(18) (</sup>a) Alexakis proposed a bridging role of the carboxylate ligand for a mixed zinc cuprate complex in a copper-catalyzed enantioselective conjugate addition. See: Alexakis, A.; Benhaim, C.; Rosset, S.; Human, M. J. Am. Chem. Soc. 2002, 124, 5262–5263. Noyori also pointed out that a sulfonamide has a similar role. See: Kitamura, M.; Miki, T.; Nakano, K.; Noyori, R. Bull. Chem. Soc. Jpn. 2000, 73, 999–1014. (b) In the present reaction, Cu(OAc)<sub>2</sub> produced significantly higher enantioselectivity and product yield than CuCl or CuBr. These results support a special role of the acetate ligand, which might derive from the bridging effect between copper and zinc atoms. (c) The possibility that a cuprate species is the actual nucleophile in the conjugate addition cannot be excluded.

<sup>(19)</sup> Copper enolate should exist under rapid equilibrium between C-enolate (C-II) and O-enolate (O-II). This equilibrium is suggested by the fact that the major diastereomer was independent of the geometry of the ketene silyl acetal in the previous copper-catalyzed aldol reaction to ketones (ref 6f), which proceeded via a copper enolate species.

<sup>(20)</sup> For a recent review of catalytic asymmetric vinylogous aldol reactions, see: Denmark, S. E.; Heemstra, J. R., Jr.; Beutner, G. L. Angew. Chem., Int. Ed. 2005, 44, 4682–4698.