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Cross-Coupling Reaction of α-Chloroketones and Organotin Enolates Catalyzed by Zinc Halides for Synthesis of γ-Diketones

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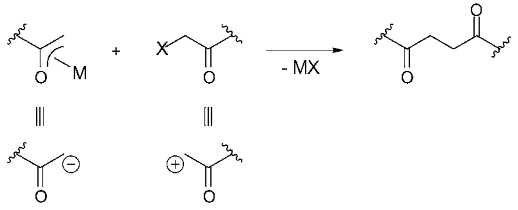
Abstract: The reaction of tin enolates **1** with α-chloro- or bromoketones **2** gave γ-diketones (1,4-diketones) **3** catalyzed by zinc halides. In contrast to the exclusive formation of 1,4-diketones **3** under catalytic conditions, uncatalyzed reaction of **1** with **2** gave aldol-type products **4** through carbonyl attack. NMR study indicates that the catalyzed reaction includes precondensation between tin enolates and α-haloketones providing an aldol-type species and their rearrangement of the oxoalkyl group with leaving halogen to produce 1,4-diketones. The catalyst, zinc halides, plays an important role in each step. The carbonyl attack for precondensation is accelerated by the catalyst as Lewis acid and the intermediate zincate promotes the rearrangement by releasing oxygen and bonding with halogen. Various types of tin enolates and α-chloro- and bromoketones were applied to the zinc-catalyzed cross-coupling. On the other hand, the allylic halides, which have no carbonyl moiety, were inert to the zinc-catalyzed coupling with tin enolates. The copper halides showed high catalytic activity for the coupling between tin enolates **1** and organic halides **7** to give γ,δ-unsaturated ketones **8** and/or **9**. The reaction with even chlorides proceeded effectively by the catalytic system.

Introduction

A metal-catalyzed cross-coupling reaction through carbon−carbon bond formation is an important and powerful method for organic synthesis.[1] In general, organometallic compounds and organic halides (or related compounds) are often the coupling partners in this type of reaction. 1,4-Diketones (γ-diketones) are widely used as synthetic building blocks for further elaboration into furans, cyclopentenones, or pyrroles.[2] In terms of applicability, the most straightforward method for their preparation would be cross-coupling of different carbonylmethyl units, namely, carbonylmethyl anion and cation equivalents (Scheme 1). Although a number of homo-coupling reactions of carbonylmethyl radicals,[3] metal enolates,[4] or α-halocarbonyls[5] were reported, the cross-coupling of carbonylmethyl units is still a challenging problem.[6] One main reason for the difficulty in the cross-coupling is ascribed to lack of appropriate compounds as carbonylmethyl cation equivalents. α-Halocarbonyls might be a typical carbonylmethyl cation equivalent, but they have a reactive site at the carbonyl carbon as well as a halogeno moiety.[7] This situation leads to a serious problem in chemoselectivity. In fact, Stille reported that the Pd-catalyzed reaction of metal enolate with α-bromoketone afforded keto oxirane that is formed through carbonyl addition.[8] Thus, many groups have developed different types of carbonylmethyl cation equivalents masked at the carbonyl moiety to avoid the undesired reaction for preparation of 1,4-diketones.[9] A versatile process to access 1,4-diketones is now the conjugate acylation of enones, and a variety of acyl anion equivalents have been developed.[10]

Scheme 1. Cross-Coupling of Carbonylmethyl Units



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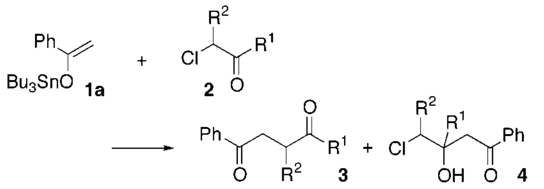
We have been studying the coupling reaction of tin enolates with α-bromocarbonyls in the presence of an equimolar amount of a ligand to the tin center.[11] In this system, highly coordinated tin enolates are generated which show high nucleophilicity for halide selective coupling.[12] However, there still remain problems to be solved: (1) catalytic reactions, (2) use of chloroketones, (3) use of cyclic haloketone, and (4) high chemoselectivity are required.[13] Recently, much attention has been focused on the metal-catalyzed cross-coupling reactions with organic chlorides, which are more available, stable, and cheap but less reactive than bromides or iodides that are commonly used as coupling partners.[14] In this paper, we report the first successful metal-*catalyzed* cross-coupling of different carbonylmethyl units using *chloroketones* as a cationic partner.[15] This method directly leads to a wide variety of 1,4-dicarbonyl compounds under mild conditions. The carbonyl moiety in chloroketone acts as a directing group for selective C−C bond formation at the chloride site. Furthermore, the metal-catalyzed coupling with allylic halides including chlorides is achieved to afford γ,δ-unsaturated ketones.

Results and Discussion

Reaction of Tin Enolates with α-Haloketones. Tin enolates readily react with aldehydes to give aldol-type products.[16] On the contrary, the substitution reaction with halides at the halogenated carbon is unlikely to occur.[17] In the reaction with α-haloketone that has both carbonyl and halide moieties, a carbonyl attack exclusively proceeds to afford halohydrin derivatives.[18] In fact, an uncatalyzed reaction of tin enolate **1a** with chloroketones **2a**−**c** gave the halohydrin derivatives **4** in high yields, not 1,4-diketones **3** (Table 1).

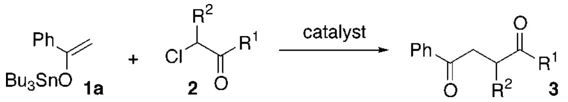
Table 1. Uncatalyzed Reaction of Tin Enolate **1a** with α-Chloroketone **2a**−**c**[a]



entry		R^1	R^2	yield/%	
1	**2a**	Ph	H	0 (**3aa**)	>99 (**4aa**)
2	**2b**	Me	H	0 (**3ab**)	62 (**4ab**)
3	**2c**	$-(CH_2)_4-$		0 (**3ac**)	>99 (**4ac**)

[a] All reactions were carried out in THF (1 mL) with tin enolate **1a** (2.0 mmol) and chloroketone **2** (1.0 mmol) at 40 °C for 6 h.

Table 2. Effects of Catalysts in the Reaction of Tin Enolate **1a** with α-Chloroketone **2a**−**c**[a]



entry		R^1	R^2	catalyst	time/h	product	yield/%
1	**2a**	Ph	H	LiCl	4	**3aa**	16[b]
2	**2a**	Ph	H	$MgCl_2$	3	**3aa**	17[b]
3	**2a**	Ph	H	$CuCl_2$	2	**3aa**	10[c]
4	**2a**	Ph	H	$AlCl_3$	1.5	**3aa**	40[b]
5	**2a**	Ph	H	$InCl_3$	6	**3aa**	31[b]
6	**2a**	Ph	H	$ZnCl_2$	2	**3aa**	>99
7	**2a**	Ph	H	$ZnBr_2$	2	**3aa**	72
8	**2a**	Ph	H	ZnI_2	4	**3aa**	72
9	**2b**	Me	H	$ZnCl_2$	2	**3ab**	64
10	**2c**	$-(CH_2)_4-$		$ZnCl_2$	2	**3ac**	82

[a] All reactions were carried out in THF (1 mL) with tin enolate **1a** (2.0 mmol), chloroketone **2** (1.0 mmol), and catalyst (0.1 mmol) at 40 °C. [b] Unidentified complicated mixture was produced in addition to the formation of **3**. [c] Starting material **2** was recovered in addition to the formation of **3**.

We found an interesting effect of metal halides as a catalyst on this type of reaction, and the results are summarized in Table 2. When a catalytic amount of LiCl was added to this reaction system, a cross-coupling product, 1,4-diketone **3aa**, was obtained in 16% yield accompanied by an unidentified complicated mixture, which was probably formed via carbonyl addition (entry 1).[19,20] $MgCl_2$ and $CuCl_2$ also gave the 1,4-diketone, though the yields were low (entries 2 and 3). Moderate yields were obtained by using $AlCl_3$ or $InCl_3$ (entries 4 and 5). Gratifyingly, zinc halides ($ZnCl_2$, $ZnBr_2$, and ZnI_2) completely altered the reaction course to give the 1,4-diketone without any other side products (entries 6−8). Only a 0.1 equiv of the catalyst was effective for the cross-couplilng reaction. THF was the best choice out of the solvents examined since toluene and acetonitrile afforded **3aa** in lower yields with $ZnCl_2$ catalyst (69% and 74%) compared with the >99% yield in entry 6. The aliphatic and cyclic chloroketones **2b** and **2c** were also applicable for the $ZnCl_2$-catalyzed system to give 1,4-diketones **3ab** and **3ac**, respectively (entries 9 and 10).

We examined the generality of the zinc-catalyzed cross-coupling reaction. Table 3 shows the effective and exclusive

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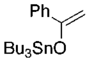
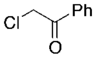
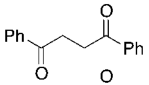
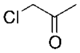
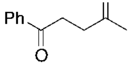
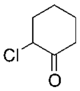
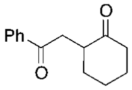
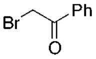
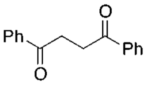
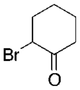
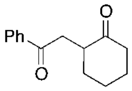
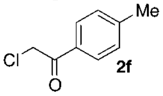
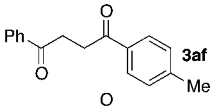
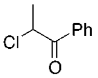
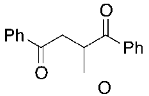
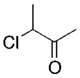
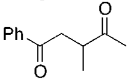
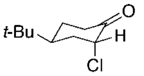
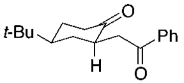
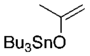
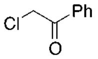
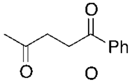
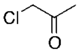
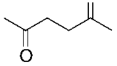
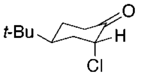
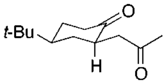
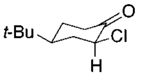
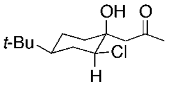
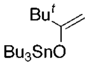
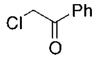
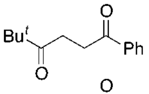
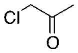
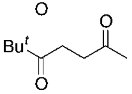
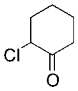
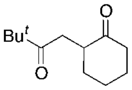
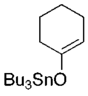
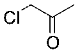
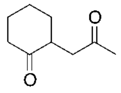
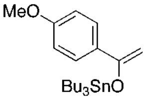
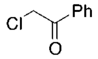
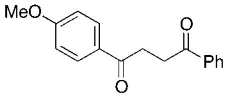
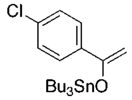
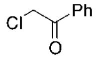
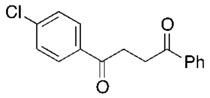
Table 3. Reaction of Tin Enolate **1** with α-Haloketone **2** Catalyzed by Zinc Halide[a]

entry	tin enolate	haloketone	catalyst	time/ h	product	yield/ %
1	 **1a**	 **2a**	$ZnCl_2$	2	 **3aa**	>99
2			$ZnBr_2$	2		72
3[b]		 **2b**	$ZnCl_2$	24	 **3ab**	84
4			$ZnCl_2$	2		64
5		 **2c**	$ZnCl_2$	6	 **3ac**	82
6			$ZnBr_2$	2		75
7		 **2d**	$ZnBr_2$	2	 **3aa**	78
8		 **2e**	$ZnBr_2$	2	 **3ac**	70
9		 **2f**	$ZnCl_2$	6	 **3af**	73
10		 **2g**	$ZnCl_2$	44	 **3ag**	74
11		 **2h**	$ZnCl_2$	28	 **3ah**	90
12		 **2i**	$ZnCl_2$	24	 **3ai**	85
13	 **1b**	 **2a**	$ZnBr_2$	24	 **3ab**	53
14		 **2b**	$ZnBr_2$	8	 **3bb**	75
15			$ZnCl_2$	24		60
16		 **2i**	$ZnCl_2$	24	 **3bi**	96
17		 **2j**	$ZnCl_2$	24	 **4bj**	20
18	 **1c**	 **2a**	$ZnCl_2$	3	 **3ca**	74
19		 **2b**	$ZnBr_2$	1.5	 **3cb**	66
20		 **2c**	$ZnBr_2$	6	 **3cc**	76
21	 **1d**	 **2b**	$ZnCl_2$	6	 **3db**	47
22	 **1e**	 **2a**	$ZnCl_2$	4	 **3ea**	75
23	 **1f**	 **2a**	$ZnCl_2$	4	 **3fa**	62

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[a] All reactions were carried out in THF (2 mL) with tin enolate **1** (2.0 mmol), haloketone **2** (1.0 mmol), and zinc halide (0.1 mmol) at 40 °C. [b] The reaction was carried out at 60 °C.

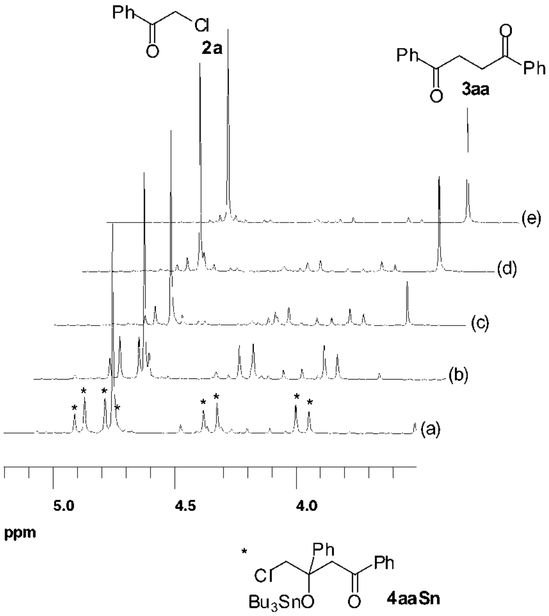


Figure 1. ^{1}H NMR spectra of the ZnCl$_2$-catalyzed reaction mixture of **1a** with **2a** in C$_6$D$_6$: (a) t = 5 min, 25 °C; (b) t = 15 min, 40 °C; (c) t = 30 min, 60 °C; (d) t = 60 min, 60 °C; and (e) t = 90 min, 75 °C.

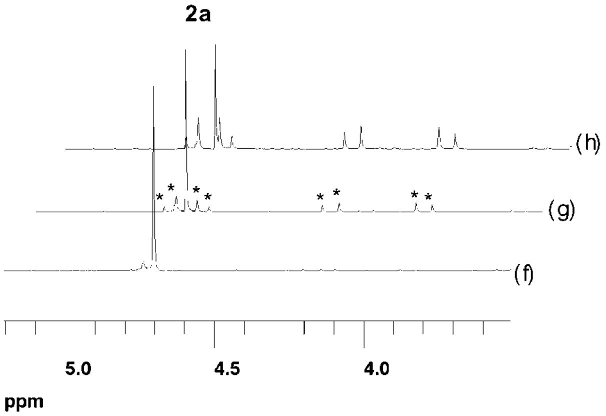
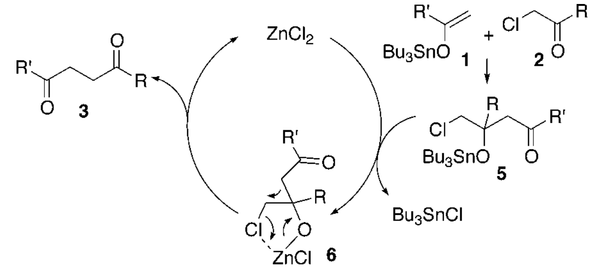


Figure 2. ^{1}H NMR spectra of the uncatalyzed reaction mixture of **1a** with **2a** in C$_6$D$_6$: (f) t = 5 min, 25 °C; (g) t = 30 min, 60 °C; and (h) t = 60 min, 60 °C.

Scheme 2



formation of 1,4-diketones **3** with various types of tin enolates **1**[21,22] and α-haloketones **2**. α-Bromoketones were also applied to this reaction system to give 1,4-diketones in high yields (entries 7 and 8). The efficient formation of 1,4-diketones from cyclic haloketones was noteworthy (entries 5, 6, 8, 12, 16, and 20), because 2-bromocyclohexanone gave not 1,4-diketone but an aldol-type product by our previous method with the highly coordinated tin enolate.[11b] Even the reactions with sterically hindered chloroketones **2g** and **2h** proceeded smoothly to give 1,4-diketones **3ag** and **3ah** in high yields (entries 10 and 11). In entry 12, *trans*-4-*tert*-butyl-2-chlorocyclohexanone (**2i**) gave a single isomer of *cis*-diketone **3ai**, whose relative configuration was unambiguously determined by X-ray analysis. High selectivity was also observed in the reaction of **1b** with **2i** (entry 16). Interestingly, the *cis*-chloroketone **2j** did not afford 1,4-diketone but aldol product **4bj** (entry 17). The use of ZnBr$_2$ sometimes showed a higher yield than the use of ZnCl$_2$ (entries 14 and 15). Tin enolates bearing electron-donating or -withdrawing substituents **1e** and **1f** showed similar reactivity with **1a** to form 1,4-diketones (entries 22 and 23).

Investigation of the Reaction Mechanism. To investigate the reaction mechanism, the reaction mixture was monitored by ^{1}H NMR. Under the same conditions as in entry 6 in Table 2, the reaction proceeded too fast to allow observation. Slightly different conditions with ZnCl$_2$ (0.1 equiv), **1a** (1.0 equiv), and **2a** (1.0 equiv) in benzene-d_6 gave an observable result as shown in Figure 1. After 5 min at 25 °C, the signals corresponding to aldol-type adduct **4aaSn**, marked by asterisks in the chart, appeared along with the starting chloroketone **2a** (Figure 1a). The increase of 1,4-diketone **3aa** with the decrease of **4aaSn** can be seen in Figure 1b−e on gradually raising the temperature from 25 to 75 °C for 90 min. In the uncatalyzed reaction as shown in Figure 2, no signal corresponding to **4aaSn** was observed in 5 min at 25 °C in Figure 2f. On raising the temperature to 60 °C, the slow formation of **4aaSn** was observed in Figure 2g and 2h. These results suggest that ZnCl$_2$ accelerates the precondensation of tin enolate with chloroketone and catalyzes the rearrangement from carbonyl adduct **4aaSn** to **3aa**.

A plausible catalytic cycle can be shown in Scheme 2. At first, tin enolate **1** adds to the α-chloroketone **2** at the carbonyl carbon to form **5**. The transmetalation of tin in **5** with zinc halide gives the reactive intermediate zincate **6**, which can readily transform to the 1,4-diketone **3** by rearrangement of the oxoalkyl group along with regeneration of zinc halide.[23,24] Generation of the zinc enolate by the transmetalation of **1** with zinc halide is also likely to occur.[25] The intermediate zincate **6** certainly plays an important role in the rearrangement, which is prompted by the affinity of zinc with halogen in **6**.[26]

The carbonyl group in **2** acts as an important directing force for coupling at the chloride site. The substitution step takes place intramolecularly due to the precondensation at the carbonyl group. In fact, no reactions were observed in the treatment of **1a** with ethyl 2-chloroacetate or allyl chloride in the presence of ZnCl$_2$, which are typical reactive organic chlorides. As shown in Scheme 3, even after completion of the uncatalyzed condensation of **1a** at the carbonyl group in **2a** under the conditions noted in entry 1 of Table 1, the addition of a catalytic amount

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(21) In general, tin enolates exist as an equilibrium mixture of keto- and/or enol-type isomers whose ratio greatly depends on the substituents. In this paper, all structures are shown as enol form for convenience.

(22) Pereyre, M.; Bellegarde, B.; Mendelsohn, J.; Valade, J. *J. Organomet. Chem.* **1968**, *11*, 97−110.

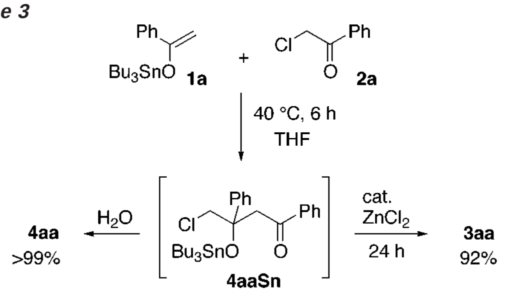
(23) (a) Nevar, N. M.; Kellin, A. V.; Kulinkovich, O. G. *Synthesis* **2000**, 1259−1262. (b) Kel'in, A. V.; Kulinkovich, O. G. *Synthesis* **1996**, 330−332.

(24) We have recently reported the rearrangement of the aryl group from the adduct which comes from α-haloketone with allylic tin(II) species. Yasuda, M.; Tsuchida, M.; Baba, A. *Chem. Commun.* **1998**, 563−564.

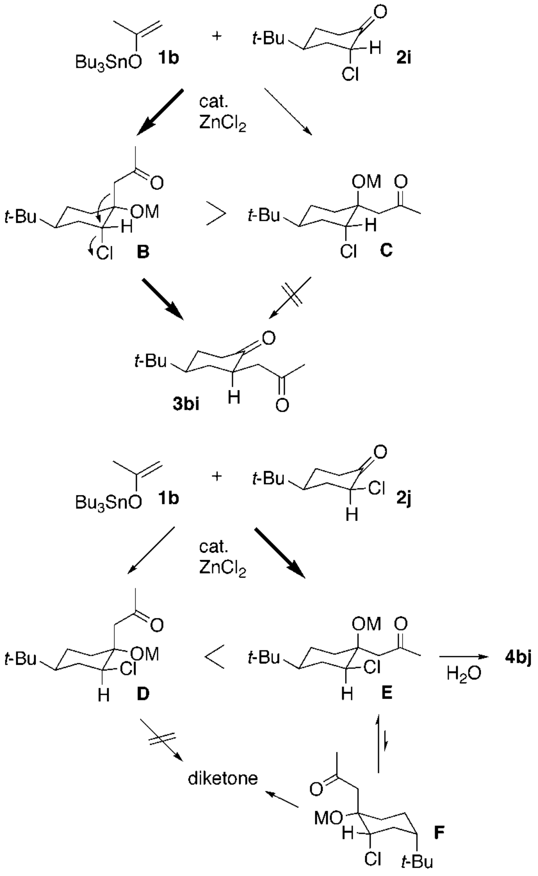
(25) A THF solution of an equiomolar mixture of **1a** and ZnCl$_2$ gave 91% of Bu$_3$SnCl at room temperature for 5 min. This result suggests fast transmetalation between tin enolate and ZnCl$_2$. In the reaction shown in Scheme 2, however, only a catalytic amount of zinc halide is used and most of the precondensation product comes from tin enolate.

(26) Katritzky, A. R.; Xie, L.; Toader, D.; Serdyuk, L. *J. Am. Chem. Soc.* **1995**, *117*, 12015−12016.

Scheme 3



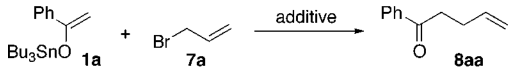
Scheme 4



of $ZnCl_2$ led to the transformation into **3aa** in high yield (92%). These results show the precondensation step should be included in the reaction course.

It is noteworthy that each diastereomer of 4-*tert*-butyl-2-chlorocyclohexanone (**2i** and **2j**) showed contrastive results (entries 16 and 17 in Table 3). These differences are clearly ascribed to the conformation of intermediate carbonyl adducts. For the formation of 1,4-diketone through the addition-rearrangement mechanism, the intermediate should have an oxoalkyl group and Cl in *anti*-periplanar positions such as **B** or **F** in Scheme 4. Therefore, the reaction of **1b** with **2i** presumably proceeds through **B** to diketone **3bi**. The facial selective addition of **1b** to **2i** via axial attack can be explained if the $ZnCl_2$ catalyst acts as does Ph_4SbBr, which was previously reported to be the catalyst for the selective formation of chlorohydrin **B** (M = H).[27] In fact, Ph_4SbBr-catalyzed reaction of **1b** with **2i** in THF for 24 h, in which **B** (M = $SnBu_3$) would be predominantly formed in situ,[18] followed by loading of a catalytic amount of $ZnCl_2$ gave exclusive formation of **3bi** in 58% yield. On the other hand, it is assumed that the reaction of **1b** with **2j** takes place via equatorial attack to give **E**, which was hydrolyzed to give **4bj**. The formation of diketone is unlikely to occur because the equilibrium between **E** and **F** largely lies on the side of **E**. The equatorial attack of tin enolate to **2j** is commonly observed; both cases of uncatalyzed and Ph_4SbBr-catalyzed reaction of **1b** with **2j** were reported to give **E** (M = H) as a single isomer.[18] The addition of $ZnCl_2$ to the reaction mixture including only **E** (M = $SnBu_3$) derived from uncatalyzed reaction of **1b** with **2j** gave no 1,4-diketone and only chlorohydrin **4bj** (M = H) in 62% yield. Since the unsubstituted 2-halocyclohexanone system has a low energy barrier between conformers, $ZnCl_2$-catalyzed reaction smoothly affords 1,4-diketone.[28]

Table 4. Effect of Additives in the Reaction of Tin Enolate **1a** with Allyl Bromide **7a**[a]



entry	additive (mmol)	time/h	yield/%
1	$ZnCl_2$ (0.1)	24	0
2	$ZnCl_2$ (1)	24	0
3	$ZnBr_2$ (1)	24	0
4	ZnI_2 (1)	24	0
5	$NiCl_2$ (1)	20	10
6	CuCl (0.1)	16	>99
7	CuBr (0.1)	16	>99
8	CuI (0.1)	16	>99
9	$CuCl_2$ (0.1)	20	80
10	$CuBr_2$ (0.1)	20	>99

[a] All reactions were carried out in THF (1 mL) with tin enolate **1a** (2.0 mmol), allyl bromide **7a** (1.0 mmol), and additive at 40 °C.

Reaction of Tin Enolates with Allylic Halides. We next turned our attention to the reaction with organic halides which have no directing group such as the carbonyl moiety in haloketones. As already mentioned above, no reactions were observed in the $ZnCl_2$-catalyzed reaction of **1a** with allyl halides. We have previously reported that >1 equiv of additive accelerates the coupling of tin enolate with allylic halides.[12] However, the catalytic cross-coupling is still a problem to be solved.[29]

Table 4 shows the effect of catalysts in the reaction of **1a** with allyl bromide **7a**. Even the use of 1 equiv of zinc halides resulted in no reaction (entries 2−4). A catalytic amount of $NiCl_2$ gave a low yield of the coupling product **8aa** (entry 5). As shown in entries 6−10, copper halides effectively catalyzed the reaction to give γ,δ-unsaturated ketone **8aa** in high yields. Copper halides could activate allylic halide to form a π-allylic complex, or generate copper enolate by transmetalation with tin enolate.[30] When the copper-catalyzed reaction of **1a** with **7a** was monitored by NMR, only the starting materials and the

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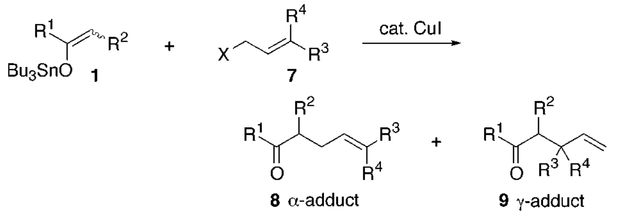
(27) We have already reported the facial selectivity of the 2-chlorocyclohexanone system with tin enolates (ref 18). The uncatalyzed reaction of **1b** with **2i** gives both isomers **B** (M = H) and **C** (M = H) in 18% and 54% yields, respectively, after workup. In the presence of a catalytic amount of Ph_4SbBr, the exclusive attack from the axial direction takes place to give **B** (M = H) as a single product in 60% yield.

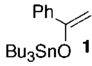
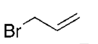
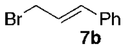
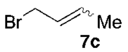
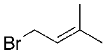
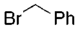
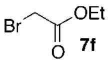
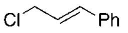
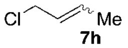
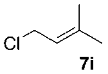
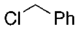
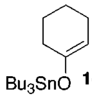
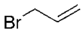
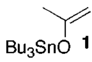
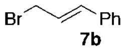
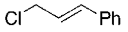
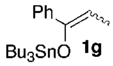
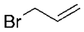
(28) 2-Chlorocyclohexanone exits as a mixture of conformers in comparable ratios: Basso, E. A.; Kaiser, C.; Rittner, R.; Lambert, J. B. *J. Org. Chem.* **1993**, *58*, 7865−7869. The $ZnCl_2$ reaction of tin enolate with either conformer gives precondensation adduct bearing Cl and an oxoalkyl group in the trans configuration as expected from the results in Scheme 4. We reported that the Ph_4SbBr-catalyzed reaction of tin enolates with 2-chlorocyclohexanone gave only the chlorohydrin with Cl and an oxoalkyl group in trans positions (ref 18).

(29) Allylic tins were reported to couple with allylic bromides in the $ZnCl_2$-catalyzed reaction. Godschalx, J. P.; Stille, J. K. *Tetrahedron Lett.* **1983**, *24*, 1905−1908.

(30) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748−2749.

Table 5. Reaction of Tin Enolates **1** with Organic Halides **7** Catalyzed by CuI[a]



entry	tin enolate	halide	time/ h	temp/ °C	yield/ % (**8** : **9**)
1	 **1a**	 **7a**	16	40	>99 (**8aa**)
2	**1a**	 **7b**	24	40	>99 (**8ab**:**9ab**; 72:28)
3	**1a**	 **7c**	16	63	>99 (**8ac**:**9ac**; 75:25)
4	**1a**	 **7d**	20	63	42 (**8ad**:**9ad**; 70:30)
5	**1a**	 **7e**	16	63	54 (**8ae**)[b]
6	**1a**	 **7f**	20	63	20 (**8af**)[c]
7	**1a**	 **7g**	20	63	88 (**8ab**:**9ab**; 67:33)
8[d]			20	63	0
9[e]	**1a**	 **7h**	20	70	86 (**8ac**:**9ac**; 76:24)
10[e]	**1a**	 **7i**	20	63	37 (**8ad**:**9ad**; 72:28)
11[e]	**1a**	 **7j**	20	70	38 (**8ae**)[b]
12	 **1d**	 **7a**	24	40	76 (**8da**)
13	 **1b**	 **7b**	24	40	>99 (**8bb**:**9bb**; 67:33)
14	**1b**	 **7g**	21	63	14 (**8bb**:**9bb**; 33:67)
15	 **1g**	 **7a**	24	40	30 (**8ga**)

[a] All reactions were carried out in THF (1 mL) with tin enolate **1** (2.0 mmol), organic halide **7** (1.0 mmol), and CuI (0.1 mmol). [b] **8ae** = 1,3-diphenyl-1-propanone. [c] **8af** = ethyl 4-oxo-4-phenylbutanoate. [d] Without CuI. [e] DMF was used as solvent instead of THF.

product were observed without any intermediates. Evidence for the generation of neither π-allylic copper nor copper enolate was obtained even in the equimolar mixture of CuI and **7a** or CuI and **1a** in THF. The reaction mechanism and the catalyst behavior are not clear at this stage.

Table 5 shows the results of coupling between various types of tin enolates **1** and organic halides **7** catalyzed by CuI. The reaction of **1a** with cinnamyl bromide **7b** gave the cross-coupling product quantitatively (entry 2). The reactions with crotyl bromide **7c** also proceeded smoothly and gave the products at 63 °C (entry 3). Moderate yields were obtained in the reaction with prenyl or benzyl bromide (entries 4 and 5). When α-bromoester **7f** was used as the substrate, the reaction resulted in low conversion (entry 6).[31] It is noteworthy that allylic chlorides were also applied to the CuI-catalyzed reaction system. The reaction with cinnamyl chloride **7g** gave the coupling products in 88% yield under THF reflux conditions, while no reaction was observed without the catalyst (entries 7 and 8). Satisfactory yield was obtained in the reaction with crotyl chloride **7h** using DMF as a solvent.[32] Other tin enolates were also applied to the CuI-catalyzed coupling to give the cross-coupling products in moderate to high yields (entries 12−15).

Conclusions

We have demonstrated the cross-coupling of carbonylmethyl units using α-chloroketones and tin enolates as coupling partners. Zinc halides showed excellent catalytic activity for the coupling. The reaction course includes the precondensation between tin enolates and α-haloketone providing an aldol-type species and rearrangement of the oxoalkyl group with substitution of halogen to produce 1,4-diketones. The carbonyl group in haloketone acts as a directing group for the coupling reaction. NMR studies apparently suggest two steps are involved in the reaction course. Zinc halides have two functions: (i) as a Lewis acid accelerating and controlling the precondensation step (formation of **5**) and (ii) as an agent promoting the rearrangement by releasing oxygen and bonding with halogen (formation of **3** from **6**). The reaction with organic halides which have no directing group was catalyzed by a different type of catalyst. The copper halides effectively catalyzed the cross-coupling of tin enolates with allylic halides to give γ,δ-unsaturated ketones. This system was also applied to chloride substrates as cationic coupling partners.

Experimental Section

General. Melting points were taken on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded as thin films or as solids in KBr pellets on a Hitachi 260-30 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained with a JEOL JNM-GSX-270 (270 and 67.9 MHz) or a JEOL JNM-GSX-400 (400 and 100 MHz) spectrometer, respectively, with TMS as internal standard. Mass spectra were recorded on a JEOL JMS-DS303 or a Shimadzu GCMS-QP2000A spectrometer. GLC analyses were performed on a Shimadzu GC-8A with FID, using a 2 m × 3 mm column packed with SE-52. Flash chromatography was performed on silica gel (Wakogel C-300). Bulb-to-bulb distillation (Kugelrohr) was accomplished in a Sibata GTO-250RS at the oven temperature and pressure indicated. Yields were determined by GLC or ^{1}H NMR with internal standards.

Materials. THF was distilled from sodium and benzophenone. Tin enolates **1a**−**d** and **1g** were prepared from tributyltin methoxide and the corresponding enol acetates by known methods.[16b,22] The tin enolates **1e** and **1f** were prepared from *p*-methoxy-α-acetoxystyrene[33] and *p*-chloro-α-acetoxystyrene[33] with tributyltin methoxide in a similar fashion.[16b,22] All tin compounds were handled carefully because of their toxicity. α-Haloketones **2a**, **2b**, **2c**, **2d**, **2f**, and **2h** were commercially available. 2-Bromocyclohexanone (**2e**),[34] 2-chloropropiophenone (**2g**),[35] and 4-*tert*-butylcyclohexanone (**2i** and **2j**)[36] were prepared according

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(31) The palladium-catalyzed coupling of haloester with tin enolate or allyltin reagents was reported. Simpson, J. H.; Stille, J. K. *J. Org. Chem.* **1985**, *50*, 1759−1760.

(32) The reaction carried out in THF under the reflux condition resulted in low yield (21%, **8ac**:**9ac**; 64:36).

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to the described methods. Allylic halides (and related halides) **7a−j** were commercial products. Zinc halides were dried under reduced pressure before use.

Uncatalyzed Reaction of Tin Enolates with Chloroketones. To a solution of a tin enolate **1** (2.0 mmol) in dry THF (1 mL) was added α-chloroketone **2** (1.0 mmol) under nitrogen. The mixture was stirred under the reaction conditions noted in Table 1 and quenched with water (5 mL). Diethyl ether (30 mL) and aqueous NH_4F (15%; 15 mL) were added and the homogeneous mixture was vigorously stirred for 20 min. The resulting Bu_3SnF was filtered off. The filtrate was washed with water (30 mL × 2), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue on silica gel gave pure products.

General Procedure for Synthesis of 1,4-Diketones (3). To a mixture of a tin enolate **1** (2.0 mmol) and 0.1 mmol of zinc halide (or other metal halides in Table 2) in dry THF (1 mL) was added α-haloketone **2** (1.0 mmol) under nitrogen. The reaction mixture was stirred under the reaction conditions noted in Table 2 or 3. Water (5 mL) was then added to the solution. Diethyl ether (30 mL) and aqueous NH_4F (15%; 15 mL) were added and the homogeneous mixture was vigorously stirred for 20 min. The resulting Bu_3SnF was filtered off. The filtrate was washed with water (30 mL × 2), dried ($MgSO_4$), and evaporated. Flash chromatography of the resultant residue on silica gel or recrystallization gave pure products.

Control Experiment for Investigation of Reaction Mechanism (Scheme 3). To a solution of tin enolate **1a** (2.0 mmol) in dry THF (1 mL) was added α-chloroketone **2a** (1.0 mmol) under nitrogen. The mixture was stirred at 40 °C for 6 h. Then $ZnCl_2$ (0.1 mmol) was added to the solution. The reaction mixture was stirred for 24 h and quenched with water (5 mL). Diethyl ether (30 mL) and aqueous NH_4F (15%; 15 mL) were added and the resulting Bu_3SnF was filtered off. The filtrate was washed with water (30 mL × 2), dried ($MgSO_4$), and evaporated to give an oil that was found by NMR and GLC analyses to consist of the compound **3aa** (92%) without **4aa**.

NMR Study of the Reaction of 1a with 2a (Figure 1). To a dry benzene-d_6 solution of $ZnCl_2$ (0.04 mmol) in an NMR tube was introduced **1a** (0.4 mmol) and **2a** (0.4 mmol). ^{1}H NMR spectra were recorded at varying temperature from 25 to 75 °C as shown in Figure 1. Noncatalyzed reaction was carried out without $ZnCl_2$ at 25−60 °C.

General Procedure for Synthesis of γ,δ-Unsaturated Ketones (8 and/or 9). To a mixture of tin enolate **1** (2.0 mmol) and a catalytic amount of CuI (0.1 mmol) in dry THF (1 mL) was added organic halide **7** (1.0 mmol) under nitrogen. The reaction mixture was stirred under the conditions noted in Table 5. Water (5 mL) was then added to the solution. Diethyl ether (30 mL) and aqueous NH_4F (15%; 15 mL) were added and the resulting Bu_3SnF was filtered off. The filtrate was washed with water (30 mL × 2), dried ($MgSO_4$), and evaporated. Flash chromatography of the resultant residue on silica gel or recrystallization gave pure products.

Spectral Data. These products **3aa**,[11b] **3ab**,[11b] **3ac**,[11b] **3ah**,[11b] **3cb**,[11b] **3cc**,[11c] **3db**,[37] **4bj**,[18b] **8aa**,[12a] **8ab**,[12a] **8ac**,[38] **9ac**,[39] **8ad**,[40] **9ad**,[41] **8ae**,[12a] **8af**,[11b] **8da**,[42] **8bb**,[12a] **9bb**,[43] and **8ga**[44] were identified by the spectral data described in the literature. The spectral data of the product **3bb** was in excellent agreement with the commercially available sample (Aldrich).

1-(4-Methylphenyl)-4-phenylbutane-1,4-dione (3af). According to the general procedure, this compound was prepared from **1a**, $ZnCl_2$, and **2f** in THF to give the product as a white solid after recrystallization (hexane): mp 114−116 °C; IR (KBr) 1680 cm^{-1}; ^{1}H NMR (270 Hz, $CDCl_3$) δ 8.06−7.22 (m, 4H, aromatic), 7.58−7.44 (m, 3H, aromatic), 7.29−7.25 (m, 2H, aromatic), 3.45 (s, 4H, 2- and 3-H_2), 2.42 (s, 3H, Me); ^{13}C NMR (67.9 Hz, $CDCl_3$) 198.77 (s), 198.28 (s), 143.90 (s), 136.81 (s), 134.30 (s), 133.08 (d), 129.24 (d), 128.55 (d), 128.22 (d), 128.10 (d), 32.60 (t), 32.46 (t), 21.63 (q); MS (EI, 70 eV) *m/z* 252 (M^+, 8), 119 (100), 105 (41); HRMS (EI, 70 eV) calcd for $C_{17}H_{16}O_2$ 252.1150, found *m/z* 252.1121, 252.1140, 252.1175 (M^+). Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.63; H, 6.32.

2-Methyl-1,4-diphenylbutane-1,4-dione (3ag). According to the general procedure, this compound was prepared from **1a**, $ZnCl_2$, and **2g** in THF to give the product as a white solid after recrystallization (hexane): mp 106 °C; IR (KBr) 2970 (alkyl), 1680, 1660 cm^{-1}; ^{1}H NMR (270 Hz, $CDCl_3$) 8.07−7.43 (m, 10H, aromatic), 4.23−4.15 (m, 1H, 2-H), 3.73 (dd, J = 8.3, 17.6 Hz, 1H, 3-H^A), 3.12 (dd, J = 4.9, 17.6 Hz, 1H, 3-H^B), 1.29 (d, J = 7.3 Hz, 3H, Me); ^{13}C NMR (67.9 Hz, $CDCl_3$) 203.33 (s, C-1), 198.41 (s, C-4), 136.64 (s), 133.14 (d), 136.06 (s), 132.92 (d), 128.62 (d), 128.52 (d), 128.48 (d), 128.05 (d), 42.30 (t, C-3), 36.23 (d, C-2), 17.91 (q, Me); MS (EI, 70 eV) *m/z* 252 (M^+, 3.5), 147 (5), 105 (100), 77 (37), 51 (12); HRMS:(EI, 70 eV) calcd for $C_{17}H_{16}O_2$ 252.1150, found *m/z* 252.1121, 252.1140, 252.1175 (M^+). Anal. Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.63; H, 6.34.

(2*R,4*S**)-4-*tert*-Butyl-2-(2-oxo-2-phenylethyl)cyclohexane-1-one (3ai)**. According to the general procedure, this compound was prepared from **1a**, $ZnCl_2$, and **2i** in THF to give the product as a white solid after recrystallization (hexane). The crystal obtained was suitable for X-ray crystallographic analysis. Details of the crystal structure data and analysis are provided in the Supporting Information: mp 133 °C; IR (KBr) 2950, 1700, 1680 cm^1; ^{1}H NMR (400 MHz, $CDCl_3$) 8.00−7.97 (m, 2H, aromatic), 7.57−7.53 (m, 1H, aromatic), 7.47−7.43 (m, 2H, aromatic), 3.62 (dd, J = 17.58, 6.35 Hz, 1H, $PhCOCH^A$), 3.21−3.16 (m, 1H, 2-H), 2.69 (dd, J = 17.58, 5.37 Hz, 1H, $PhCOCH^B$), 2.47−2.43 (m, 2H), 2.21−2.13 (m, 2H), 1.74−1.67 (m, 1H), 1.54−1.42 (m, 1H), 1.32−1.22 (m, 1H), 0.92 (s, 9H, CMe_3); ^{13}C NMR (100 MHz, $CDCl_3$) 211.79 (s), 198.48 (s), 137.01 (s), 132.92 (d), 128.45, (d), 128.00 (d), 46.94 (d), 45.48 (d), 41.16 (t), 38.44 (t), 35.19 (t), 32.36 (s), 28.61 (t), 27.58 (q); MS (EI, 70 eV) *m/z* 272 (M^+, 18), 215 (35), 153 (64), 133 (18), 120 (33), 105 (100), 77 (27), 57 (22); HRMS (EI, 70 eV) calcd for $C_{18}H_{24}O_2$ 272.1776, found *m/z* 272.1801, 272.1788, 272.1746 (M^+). Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.49; H, 8.89.

(2*R,4*S**)-4-*tert*-Butyl-2-(2-oxopropyl)cyclohexane-1-one (3bi)**. According to the general procedure, this compound was prepared from **1b**, $ZnCl_2$, and **2i** in THF to give the product as a colorless liquid after flash chromatography (hexane/Et_2O, 1/1) and distillation: bp 115 °C/1 mmHg; IR (KBr) 2950, 1710, 1700 cm^1; ^{1}H NMR (400 MHz, $CDCl_3$) 3.05−2.93 (m, 2H), 2.42−2.35 (m, 2H), 2.21 (s, 3H, MeC═O), 2.20−1.10 (m, ring), 0.90 (s, 9H, CMe_3); ^{13}C NMR (100 MHz, $CDCl_3$) 211.79 (s), 207.28 (s), 46.94 (d), 45.59 (d), 43.31 (t), 41.07 (t), 34.93 (t), 32.35 (s, Me_3*C*), 30.42 (q, *Me*CO), 28.53 (t), 27.58 (q, *Me*$_3$C); MS (EI, 70 eV) *m/z* 167 ($M^+ - 43$, 18), 153 (20), 111 (20), 57 (63), 43 (100). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 70.49; H, 10.29.

5,5-Dimethyl-1-phenylhexane-1,4-dione (3ca). According to the general procedure, this compound was prepared from **1c**, $ZnCl_2$, and **2a** in THF to give the product as a colorless liquid after flash chromatography (hexane/Et_2O, 10/1) and distillation: bp 125 °C/1 mmHg; IR (neat) 1680, 1660 cm^{-1}; ^{1}H NMR (400 Hz, $CDCl_3$) 7.99−7.46 (m, 5H, aromatic), 3.26 (t, J = 6.4 Hz, 2H, 2-H_2), 2.97 (t, J = 6.4

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Hz, 2H, 3-H_2), 1.22 (s, 9H, Bu^t); ^{13}C NMR (100 Hz, $CDCl_3$) 214.66 (C-4), 198.96 (C-1), 136.88, 133.05, 128.56, 128.06, 44.07, 32.42, 30.77, 26.64 (5-Me_3); MS (CI, 70 eV) *m*/*z* 219 (M^+ + 1, 100), 161 (57), 133 (13), 105 (16); HRMS (CI, 70 eV) calcd for $C_{12}H_{20}O_2$ 219.3037, found *m*/*z* 219.1370, 219.1394, 219.1376 (M^+ + 1). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.98; H, 8.38.

1-(4-Methoxyphenyl)-4-phenylbutane-1,4-dione (3ea) According to the general procedure, this compound was prepared from **1e**, $ZnCl_2$, and **2a** in THF to give the product as a yellow solid after recrystallization (hexane/benzene, 3/1): mp 98−100 °C; IR (KBr) 1692, 1673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 8.05−8.00 (m, 4H, aromatic), 7.57−7.46 (m, 3H, aromatic), 6.96−6.93 (m, 2H, aromatic), 3.88 (s, 3H, Me), 3.47−3.39 (m, 4H, 2-H_2 and 3-H_2); ^{13}C NMR (100 MHz, $CDCl_3$) 198.85, 197.14, 163.50 (*C*-OMe), 136.81, 133.06, 130.35, 129.87, 128.55, 128.09, 113.70, 55.43 (Me), 32.63, 32.19; MS (EI, 70 eV) *m*/*z* 268 (M^+, 40), 135 (100), 105 (20), 77 (16); HRMS (EI, 70 eV) calcd for $C_{17}H_{16}O_3$ 268.1099, found *m*/*z* 268.1084, 268.1108, 268.1107 (M^+). Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.38; H, 6.19.

1-(4-Chlorophenyl)-4-phenylbutane-1,4-dione (3fa). According to the general procedure, this compound was prepared from **1f**, $ZnCl_2$, and **2a** in THF to give the product as a white solid after recrystallization (hexane/benzene, 3/1): mp 114 °C; IR (KBr) 1670, 1660 cm^1; ^1H NMR (400 MHz, $CDCl_3$) 8.05−7.96 (m, 4H, aromatic), 7.60−7.56 (m, 1H, aromatic), 7.50−7.44 (m, 4H, aromatic), 3.49−3.40 (m, 4H, 2-H_2 and 3-H_2); ^{13}C NMR (100 MHz, $CDCl_3$) 198.48, 197.47, 139.57, 136.65, 135.11, 133.22, 129.53, 128.91, 128.61, 128.10, 32.53, 32.49; MS (EI, 70 eV) *m*/*z* 272 (M^+, 53), 139 (59), 133 (13), 111 (13), 105 (100), 77 (23); HRMS (EI, 70 eV) calcd for $C_{16}H_{13}O_2Cl$ 272.0604, found *m*/*z* 272.0603, 272.0633, 272.0604 (M^+). Anal. Calcd for $C_{16}H_{13}O_2Cl$: C, 70.46; H, 4.80; Cl, 13.00. Found: C, 70.25; H, 4.82; Cl, 13.28.

1,3-Diphenyl-4-pentene-1-one (9ab). According to the general procedure, this compound was prepared from **1a**, CuI, and **7b** in THF. The title compound was obtained with **8ab** and separated by flash chromatography (hexane/Et_2O, 20/1) and distillation: bp 152 °C/1 mmHg; IR (KBr) 3090, 1700, 1620 cm^1; ^1H NMR (270 MHz, $CDCl_3$) 7.94−7.90 (m, 2H, aromatic), 7.57−7.17 (m, 8H, aromatic), 6.11−5.98 (m, 1H, 4-H), 5.07 (d, *J* = 6.84 Hz, 1H, CH═CHH_1), 5.08−4.99 (m, 2H, 5-H_2), 4.18−4.10 (m, 1H, 3-H), 3.44 (dd, *J* = 16.6, 7.8 Hz, 1H, 2-H^A), 3.35 (dd, *J* = 16.6, 6.8 Hz, 1H, 2-H^B); ^{13}C NMR (67.9 MHz, $CDCl_3$) 197.99, (s, C-1), 142.99 (s), 140.57 (d, C-4) 136.97 (s), 132.85 (d), 128.42 (d), 127.90 (d), 127.58 (d), 126.39 (d), 114.54 (t, C-5), 44.36 (d, C-3), 43.83 (t, C-2); MS (EI, 70 eV) *m*/*z* 236 (M^+, 9), 117 (12), 105 (100), 77 (21); HRMS (EI, 70 eV) calcd for $C_{17}H_{16}O$ 236.1201, found *m*/*z* 236.1189, 236.1195, 236.1196 (M^+). Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.82. Found: C, 86.35; H, 6.87.

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Supporting Information Available: Experimental details and tables for X-ray crystal structures of **3ai** (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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