(13). 12 (0.0549 g, 0.244 mmol) and acetone (0.0297 g, 0.512 mmol), SmI_2 (0.5121 mmol), 5 h, −78 to 25 °C. Amide 13 was isolated (0.0161 g, 46%) as a yellow oil by flash chromatography on silica gel (2:1 EtOAc–hexanes). Capillary GC analysis indicated that the product was formed as a single diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.78 (s, 1 H), 5.82 (s, 1 H), 3.51–3.38 (m, 2 H), 3.37–3.15 (m, 2 H), 2.63–2.50 (m, 1 H), 2.19–2.08 (m, 1 H), 1.78–1.57 (m, 4 H), 1.44–1.39 (m, 1 H), 1.22 (s, 3 H), 1.21 (s, 3 H), 1.09 (s, 3 H), 1.23–1.04 (m, 6 H), 1.03 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 180.25, 83.99, 77.21, 69.85, 50.60, 43.99, 41.46, 32.42, 31.18, 28.60, 27.79, 19.81, 17.09; IR ($CHCl_3$) 3331.2 (br), 2968.4 (s), 2933.0 (m), 2879.9 (w), 1590.5 (s), 1453.3 (m), 1395.8 (m), 1382.5 (m), 1356.0 (m), 1263.1 (w), 1152.1 (m), 1121.5 (m), 1064.0 (w), 962.2 (w), 895.8 (w) cm^{-1}; exact mass calcd for $C_{16}H_{29}NO_2$ (M − 18) 267.2198, found 267.2213.

Acknowledgment. We are grateful to Curt Haltiwanger for performing the X-ray crystal structure determinations. We also acknowledge the National Institutes of Health for their generous support of this research.

Supplementary Material Available: Experimental data for X-ray structure determination of compounds **2f** and **5** and ^{1}H and/or ^{13}C NMR spectra for compounds **2a–d,k–l**, **7**, **11**, and **13** (41 pages). Ordering information is given on any current masthead page.

The Direct Formation of Functionalized Alkyl(aryl)zinc Halides by Oxidative Addition of Highly Reactive Zinc with Organic Halides and Their Reactions with Acid Chlorides, α,β-Unsaturated Ketones, and Allylic, Aryl, and Vinyl Halides

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Highly reactive zinc, prepared by the lithium naphthalenide reduction of $ZnCl_2$, readily undergoes oxidative addition to alkyl, aryl, and vinyl halides under mild conditions to generate the corresponding organozinc compounds in excellent yields. Significantly, the reaction will tolerate a spectrum of functional groups on the organic halides. Accordingly, this approach can now be used to prepare a wide variety of highly functionalized organozinc compounds. In the presence of Cu(I) salts, the organozinc compounds cross-couple with acid chlorides, conjugatively add to α,β-unsaturated ketones, and regioselectively undergo S_N2' substitution reactions with allylic halides. They also cross-couple with aryl or vinyl halides with Pd(0) catalysts.

Introduction

Organozinc compounds were first prepared by Frankland[1] in 1848 by oxidative addition of zinc metal to alkyl iodides. The reaction was limited due to the low reactivity of the metal. Several methods have been used to activate zinc, such as washing with HCl solution,[2] ultrasound irradiation,[3] using a Zn–Cu couple,[4] adding 1,2-dibromoethane[5] or trimethylchlorosilane[6] to the reaction mixture, and metal–solvent cocondensation.[7] In spite of these methods, the direct oxidative addition of zinc metal to organic halides has been limited to relatively reactive halides such as alkyl iodides or α-halo esters.[8] Recently, zinc homoenolates of alkyl propionates were prepared by ring-opening reactions of 1-siloxy-1-alkoxycyclopropanes.[9] However, most alkyl bromides and chlorides and all vinyl and aryl halides have been totally useless for the direct reaction with zinc metal. For these substrates, the only option was a metathesis reaction with a Grignard reagent or organolithium reagent which precluded the presence of most functional groups.

Table I. Preparation of Organozinc Compounds[a]

$$RX + Zn^* \xrightarrow[THF]{\text{temp, time}} RZnX$$

entry	organic halide	Zn*:RX ratio	time, °C	time, h	yield,[b] %
1	$Br(CH_2)_6Cl$	1.2:1	23	4	100
2	$Br(CH_2)_7CH_3$	1.2:1	23	6	100
3	$Br(CH_2)_3CO_2Et$	1:1	23	3	100
4	p-IC_6H_4Cl	2:1	23	3	100
5	p-BrC_6H_4CN	2:1	reflux	3	90
6	p-BrC_6H_6CN	3:1	reflux	3	100
7	p-$BrC_6H_4CO_2Et$	2:1	reflux	2	100
8	o-$BrC_6H_4CO_2Et$	2:1	reflux	2	100
9	m-$BrC_6H_4CO_2Et$	3:1	reflux	4	100
10	$Cl(CH_2)_3CO_2Et$	3:1	reflux	4	100[c]

[a] THF was used as solvent. [b] The percent yield was determined by GC after hydrolysis with dilute HCl solution. [c] In the presence of 2 equiv of KI.

In this paper, we would like to report that highly reactive zinc[10] prepared by the lithium naphthalenide reduction of $ZnCl_2$ readily undergoes oxidative addition to alkyl, aryl, and vinyl halides under mild conditions to generate the corresponding organozinc compounds. Significantly, the reaction will tolerate a wide spectrum of functional groups on the organic halides. We also report a variety of cross-coupling reactions of the functionalized organozinc

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(2) (a) Hauser, C. R.; Breslow, O. S. *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 408. (b) Newman, M. S.; Arens, F. J. *J. Am. Chem. Soc.* **1955**, *77*, 946.
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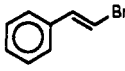
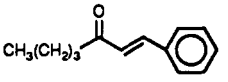
Table II. Reactions of Organozinc Halides Mediated by Copper with Acid Chlorides

$$RX + Zn^* \rightarrow [RZnX] \xrightarrow{CuCN\cdot 2LiBr} [RCu(CN)ZnX] \xrightarrow{R'COCl} RCOR'$$

no.	RX	R'COCl	Zn*:RX:R'COCl[a]	product	% yield[b]
1	$Br(CH_2)_7CH_3$	PhCOCl	1.5:1.0:0.9	$PhCO(CH_2)_7CH_3$	92
2	$Br(CH_2)_6CN$	PhCOCl	1.1:1.0:0.8	$PhCO(CH_2)_6CN$	94
3	$Br(CH_2)_6Cl$	PhCOCl	1.0:1.0:1.0	$PhCO(CH_2)_6Cl$	85
4	$BrCH_2CH_2Ph$	PhCOCl	1.2:1.0:0.9	$PhCOCH_2CH_2Ph$	97
5	$Br(CH_2)_3CO_2Et$	$CH_3(CH_2)_3COCl$	1.0:1.0:0.9	$CH_3(CH_2)_3CO(CH_2)_3CO_2Et$	91
6	$Br(CH_2)_3CO_2Et$	PhCOCl	1.0:1.0:0.9	$PhCO(CH_2)_3CO_2Et$	95
6'	$Cl(CH_2)_3CO_2Et$	PhCOCl	3.0:1.0:0.9	$PhCO(CH_2)_3CO_2Et$	91
7	p-BrC_6H_4Me	$CH_3(CH_2)_3COCl$	3.5:1.0:0.9	$CH_3(CH_2)_3COC_6H_4$-p-Me	86
8	p-$IC_6H_4CO_2Et$	$CH_3(CH_2)_3COCl$	2.0:1.0:1.0	$CH_3(CH_2)_3COC_6H_4$-p-(CO_2Et)	83
9	p-IC_6H_4Cl	$CH_3(CH_2)_3COCl$	1.5:1.0:1.0	$CH_3(CH_2)_3COC_6H_4$-p-Cl	90
10	p-$IC_6H_4CO_2Et$	PhCOCl	2.0:1.0:1.0	$PhCOC_6H_4$-p-(CO_2Et)	88
11	m-$BrC_6H_4CO_2Et$	PhCOCl	4.0:1.0:0.9	$PhCOC_6H_4$-m-(CO_2Et)	83
12	o-$BrC_6H_4CO_2Et$	PhCOCl	2.0:1.0:0.9	$PhCOC_6H_4$-o-(CO_2Et)	92
13	o-$BrC_6H_4CO_2Et$	$CH_3(CH_2)_3COCl$	2.0:1.0:0.9	$CH_3(CH_2)_3COC_6H_4$-o-$CO_2Et)$	94
14	p-BrC_6H_4CN	$CH_3(CH_2)_3COCl$	2.5:1.0:1.0	$CH_3(CH_2)_3COC_6H_4$-p-CN	71
15	p-BrC_6H_4CN	PhCOCl	3.0:1.0:0.9	$PhCOC_6H_4$-p-CN	73
16	o-BrC_6H_4CN	PhCOCl	3.0:1.0:0.9	$PhCOC_6H_4$-o-CN	98
17	o-BrC_6H_4CN	$CH_3(CH_2)_3COCl$	3.0:1.0:0.9	$CH_3(CH_2)_3COC_6H_4$-o-CN	97
18	p-$BrC_6H_4COCH_3$	$CH_3(CH_2)_3COCl$	2.0:1.0:0.9	$CH_3(CH_2)_3COC_6H_4$-p-$(COCH_3)$	80
19		$CH_3(CH_2)_3COCl$	3.0:1.0:0.9		82
20	$PhCH_2Cl$	PhCOCl	1.5:1.0:0.9	$PhCOCH_2Ph$	81
21	$Br(CH_2)_4Br$	PhCOCl	3.0:1.0:2.0	$PhCO(CH_2)_4COPh$	78
22	p-IC_6H_4I	CH_3COCl	3.0:1.0:2.0	$CH_3COC_6H_4$-p-$(COCH_3)$	76

[a] Mole ratio. [b] Isolated yield.

compounds with acid chlorides, α,β-unsaturated ketones, allylic halides, and aryl or vinyl halides.

Several methods have been reported by our group[11] for the preparation of active metals. The initial method used for the preparation of active zinc involved the reduction of anhydrous zinc halide salts with either potassium or sodium in refluxing tetrahydrofuran (THF) or 1,2-dimethoxyethane (DME). The zinc powders produced by this method readily formed alkylzinc compounds from alkyl bromides. The zinc powders also reacted with aryl bromides and iodides at refluxing temperatures. A second approach involved the reduction of anhydrous zinc halides with 2.1 equiv of lithium in THF or DME in the presence of a catalytic amount of naphthalene (10 mol % based on lithium) as an electron carrier. This approach resulted in an even more reactive zinc powder. Conclurrent with this work, it was found that reduction of a solution of zinc halides (1.0 equiv) with a preformed solution of lithium naphthalenide (2.1 equiv) in THF also provided a highly reactive form of active zinc. The last two methods not only yield a more reactive zinc metal but also utilize the much safer and convenient reducing metal lithium. The bulk of the work reported in this manuscript utilizes the third method for preparation of highly reactive zinc. The highly reactive zinc was found to readily react with alkyl or aryl iodides and bromides to yield functionalized organozinc species directly (eq 1 and Table I). In the presence of potassium iodide, organozinc species can be formed from alkyl chlorides and active zinc. It is assumed that the alkyl chloride first undergoes halogen exchange and then the organozinc is formed from the resulting alkyl iodide.

Organozinc halides have been used in the past in a variety of synthetic manipulations.[12] The work to be discussed here involves the use of organozinc species for the formation of ketones via the cross-coupling reactions of organozinc halides with acid chlorides (eq 2 and Table II), 1,4-additions to α,β-unsaturated ketones (eq 3 and Table III), regioselective reactions with allylic halides (eq 4 and Table IV), and cross-coupling reactions with vinyl and aryl halides (eq 5 and Table V).

$$Zn^* + RX \xrightarrow[\text{rt to reflux}]{THF} RZnX \quad (1)$$

$$RZnX + R'COCl \xrightarrow[THF]{CuCN\cdot 2LiBr} RCOR' \quad (2)$$

$$RZnX + \alpha,\beta\text{-enone} \xrightarrow[BF_3\cdot Et_2O]{CuCN\cdot 2LiBr} \text{1,4-adduct} \quad (3)$$

$$RZnX + \text{allylic halide} \xrightarrow[THF]{CuCN\cdot 2LiBr} S_N2' + S_N2 \quad (4)$$

$$RZnX + ArX \xrightarrow[THF]{Pd(PPh_3)_4} RAr \quad (5)$$

Results and Discussion

1. Preparation of Active Zinc and Organozinc Halides. The reduction of zinc halides with lithium and 10 mol % naphthalene requires vigorous stirring for about 10 h to give the active zinc slurry. The stirring is necessary to prevent the reduced zinc from coating and surface of the lithium and stopping the reduction. The third reduction method greatly shortens the reduction time and eliminates the zinc coating problem. This method requires two steps. The first step, which takes about 2 h, is the preparation of the dark green lithium naphthalenide/THF solution. In the second step, the zinc halide/THF solution is slowly transferred via a cannula into the lithium naphthalenide solution. The appearance of the active zinc

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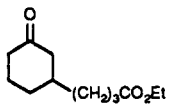
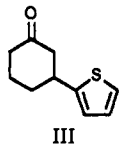
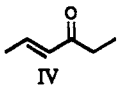
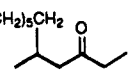
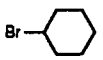
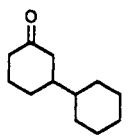
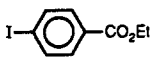
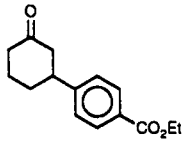
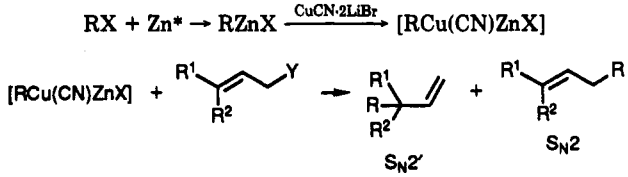
(12) (a) Negishi, E. *Organometallics in Organic Synthesis* New York: Wiley, 1980. (b) Nesmeyanov A. N.; Kocheshkov, K. A. (General Editors) *Methods of Elemento-Organic Chemistry*, Vol III; Sheverdina, N. I., Kocheshkov, K. A., Eds.; Translated from Russian by Scripta Technica, LTD. North-Holland Publishing Company: Amsterdam, 1967.

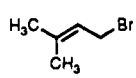
Table III. Copper-Mediated Conjugate Addition Reaction of Organozinc Halide with α,β-Unsaturated Ketones

entry	organic halide	enone	Cu(I)[a]	additives[b]	products	% yield[c]
1	$Br(CH_2)_3CO_2Et$	 I	A	$BF_3{\cdot}OEt_2$ TMSCl	 II	92 (74)
2	$Br(CH_2)_3CO_2Et$	I	A	TMSCl	II	75
3	$Br(CH_2)_3CO_2Et$	I	B	TMSCl	II	76 (55)
					 III	9 (8)
4	$Br(CH_2)_3CO_2Et$	I	B	$BF_3{\cdot}OEt_2$	III	59 (39)
					II	10
5	$Br(CH_2)_6Cl$	 IV	A	$BF_3{\cdot}OEt_2$ TMSCl		72 (77)
6		I	A	$BF_3{\cdot}OEt_2$ TMSCl		58 (66)
7		I	A	$BF_3{\cdot}OEt_2$ TMSCl		68

[a] Reactions were performed in the presence of 0.9 equiv of the following copper salts: (A) CuCN·2LiBr in THF or (B) lithuim 2-thienylcyanocuprate (0.25 M solution in THF) purchased from Aldrich. [b] Added at −78 °C just prior to the addition of enone. [c] GC yield (isolated yield).

Table IV. Reactions of RZnX with Allylic Halides Mediate by CuCN•2LiBr



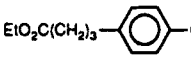
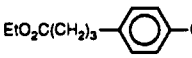
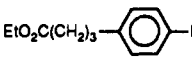
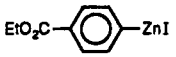
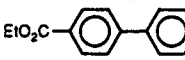
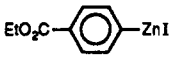
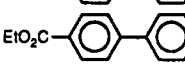
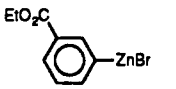
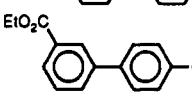
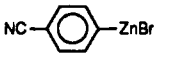
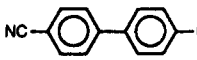
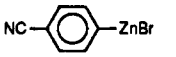
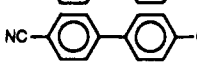
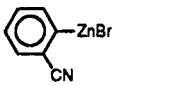
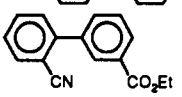
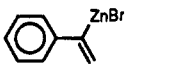
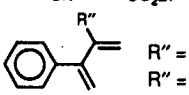
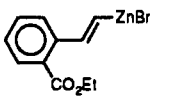
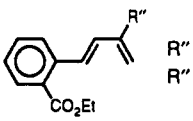
no.	RX	allylic halide	products[a] S_N2':S_N2	% yield[b]
1	$Br(CH_2)_3CO_2Et$		96:4	83
2	$Br(CH_2)_6CN$		97:3	91
3	$Br(CH_2)_6Cl$		98:2	94
4	p-$BrC_6H_4CO_2Et$		80:20	86
5	$Br(CH_2)_3CO_2Et$		100:0	87
6	$Br(CH_2)_6CN$		97:3	87
7	p-$IC_6H_4CO_2Et$		100:0	93
8	$Br(CH_2)_3CO_2Et$		97:3	86
9	$Br(CH_2)_6CN$		98:2	88
10	$Br(CH_2)_2Ph$		95:5	94
11	$Br(CH_2)_3CO_2Et$		98:2	88
12	$Br(CH_2)_6CN$		95:5	90
13	$Br(CH_2)_2Ph$		95:5	89

[a] Ratio was determined from the crude product by ^1H NMR. [b] Isolated yield.

formed depends on the amount of zinc halide added to the lithium naphthalenide and on the speed of the addition. A slow addition, about 3 s per drop with no excess of zinc halide, results in an extremely fine black slurry of active zinc. This slurry takes several hours to settle and can easily be transferred by a cannula. With faster addition, about 1 s or less per drop, the active zinc formed is sponge shaped. The solvent can be changed very easily by a cannula if further reaction needs a different solvent. The active zinc, prepared by both methods described above, has similar reactivity. The activities of zinc prepared from $ZnCl_2$, $ZnBr_2$, or ZnI_2 are similar. In this paper, the active zinc was prepared primarily from $ZnCl_2$. Naphthalene was used as the electron-transfer agent. Other electron carriers such as biphenyl or anthracene can also be used. The reactivity of the zinc prepared in THF or DME appears to be identical. Some practical considerations should be taken into account when choosing THF or DME. For instance, DME should be used if higher reaction temperatures are needed. However, the formation of lithium

Table V. Coupling Reactions of RZnX with Aryl and Vinyl Halides Catalyzed by $Pd(PPh_3)_4$

$$RZnX + R'Y \xrightarrow[THF]{5\ mol\ \%\ Pd(PPh_3)_4} RR'$$

no.	RZnX	R'Y	product	% yield[a]
1.	$EtO_2C(CH_2)_3ZnBr$	p-$BrC_6H_4COCH_3$		86
2.	$EtO_2C(CH_2)_3ZnBr$	p-BrC_6H_4CN		93
3.	$EtO_2C(CH_2)_3ZnBr$	p-$BrC_6H_4NO_2$		90
4.		p-BrC_6H_4CN		80
5.		p-$IC_6H_4CO_2Et$		94
6.		p-BrC_6H_4CN		82
7.		p-BrC_6H_4CN		95
8.		p-$IC_6H_4CO_2Et$		82
9.		m-$BrC_6H_4CO_2Et$		93
10.			 R'' = H	85 (91)
11.			R'' = CH_3	86
12.			 R'' = H	95
13.			R'' = CH_3	93

[a] Isolated yields. GC yields are shown in parentheses.

naphthalenide is much more facile in THF than in DME. Use of DME requires at least 2 h longer than THF. $ZnCl_2$ is also highly soluble in THF. This allows for the convenient transfer of the $ZnCl_2$ solution to the lithium naphthalenide solution via a cannula. If DME is chosen as the solvent, transfer of the lithium naphthalenide to $ZnCl_2$ should be done slowly or the reactivity of the zinc powder is decreased. The commercially available zinc chloride *N,N,N',N'*-tetramethylethylenediamine complex ($ZnCl_2$·TMEDA) has been used as a relatively nonhygroscopic substitute for $ZnCl_2$ in many instances. Unlike $ZnCl_2$, $ZnCl_2$·TMEDA is slightly soluble in THF. Reduction of this complex gave active zinc with reactivity similar to the active zinc prepared from anhydrous $ZnCl_2$. No enhancement in the reactivity of the active zinc was observed using this complex, and little use was made of zinc prepared from this complex.

The highly reactive zinc was allowed to react with alkyl bromides (entries 1–3, Table I) in a 1–1.2 to 1 molar ratio at room temperature for 3–6 h to give the corresponding organozinc derivatives in 100% GC yields. The formation of the organozinc species was monitored by GC and was based on the reduced product peak after hydrolysis with dilute HCl solution. The active zinc reacted with aryl iodides or bromides (entries 4–5, Table I) in a 2:1 molar ratio at room temperature to reflux in 2–3 h to give the corresponding organozinc derivatives in 90–100% yield. By increasing the mole ratio of Zn*/RX, 100% of RX can be converted to RZnX (entries 5 an 6, Table I). The ortho, meta, and para functionalized aryl halides reacted with zinc to give the corresponding ortho-, meta-, and para-substituted organozinc compounds (entries 7–9, Table I, and entries 10–12, Table II). No scrambling of positions was observed. There is no direct oxidative addition of active zinc to alkyl or aryl chlorides. But in the presence of KI under reflux conditions, alkylzinc species can be formed from alkyl chlorides and zinc. This reaction presumably involves halogen exchange prior to organozinc formation (entry 10, Table I). One significant aspect of this work is that functionalized organozinc compounds can now be readily prepared from organic halides containing ester, nitrile, acetyl, and other halides. The organozinc halide solutions are light to dark brown in color and are stable under an argon atmosphere. The excess zinc can be easily separated from the organozinc species by allowing the zinc to settle out of solution for 1–3 h and then transferring the clear organozinc solution via a cannula to another flask for further reaction.

2. Reactions of RZnX with Acid Chlorides and Enones. Knochel[13] has recently reported that organozinc iodides can be converted into the corresponding copper derivatives RCu(CN)ZnI by adding the soluble salt CuCN·2LiCl. This organometallic species reacts with various electrophiles to give the corresponding cross-coupled products in high yields. Our work has greatly expanded this approach and provides a very efficient way to prepare highly functionalized dialkyl ketones, diaryl ketones, mixed alkyl aryl ketones, and vinyl ketones. In the cross-coupling reactions with acid chlorides, excess zinc must be removed from the organozinc solution as it will react with the acid chlorides, resulting in homocoupling of acid chlorides.[14] Organozinc compounds couple with acid chlorides very

(13) (a) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2392. (b) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *Tetrahedron Lett.* **1988**, *29*, 2395. (c) Yeh, M. C. P.; Knochel, P.; Bulter, W. M.; Berk, S. C. *Tetrahedron Lett.* **1988**, *29*, 6693.

(14) (a) Wehmeyer, R. M.; Rieke, R. D. *Tetrahedron Lett.* **1988**, *29*, 4513. (b) Wu, T.-C.; Wehmeyer, R. W., private communication.

rapidly to give the cross-coupled products in good to excellent yields. For example, (*o*-cyanophenyl)zinc bromide reacts with acid chlorides to give quantitative yields of coupling products (entries 16 and 17, Table II). The reaction of *trans*-styrene-β-zinc bromide with acid chloride to yield vinyl ketones provided an important routine to synthesize vinyl ketones (entry 19, Table II). Diorganozinc bromides and iodides can also be prepared and react with acid chlorides to give diketones in good yield (entries 21 and 22, Table II). Significantly, this approach yields highly functionalized ketones not attainable by standard methods.

According to Kjonaas,[15] a general study involving the reactions of RZnX or R_2Zn with α,β-unsaturated ketones is lacking. Luche[16] has reported the efficient conjugate addition of alkyl halides to α,β-unsaturated ketones mediated by a Zn/Cu couple in aqueous media and suggested that this process occurs via a radical mechanism rather than by the free organometallic species. Lithium[17] and magnesium[15] triorganozincates undergo 1,4-additions with α,β-unsaturated ketones. However, only one of the three organic moieties is transferred in the process. This problem has been solved to some degree by utilizing only 1 equiv of the alkyllithium and 2 equiv of methyllithium in forming these reagents.[18] The methyl group appears to be a good, nontransferable "dummy" ligand for the lithium trialkylzincates. However, since trialkylzincate reagents are derived from the Grignard or lithium precursors, they offer no distinct advantage over the various types of cuprate reagents. Copper(I) salts are widely used to mediate the 1,4-addition of organozinc species to α,β-unsaturated ketones.[13] As seen in the work described above, convenient methods for forming the organozinc species are very important to the utility of these reagents in the synthetic transformation. Active zinc allows a straightforward preparation of these reagents.

Several variations were attempted using (3-carbethoxypropyl)zinc bromide as a target in order to optimize the 1,4-addition process. The best approach involved forming the zinc cuprate from the soluble CuCN/LiBr complex according to Knochel's procedure.[13] A 92% yield (GC) of 1,4-adduct was obtained (entry 1, Table III). Another approach taken in an effort to optimize the conjugate addition process was the formation of the so-called "higher order" cuprate species, as developed by Lipshutz.[19] Based on this chemistry, we have attempted to prepare a similar "higher order" cuprate species from lithium 2-thienylcyanocuprate in conjunction with the organozinc compounds (eq 6).

$$\text{LiCu(CN)2-th} + \text{RZnX} \rightarrow \text{"R(2-th)Cu(CN)ZnX"} \quad (6)$$

Substituting lithium 2-thienylcyanocuprate for the CuCN/LiBr complex, and omitting boron trifluoride etherate from the reaction of the organozinc halide species with 2-cyclohexenone, indeed gave a reasonable yield (76% GC) of the 1,4-adduct (entry 3, Table III). The reaction rate, temperature, and yield were similar to the reactions employing CuCN/LiBr. However, contrary to all previous reports by Lipshutz, a noticeable amount (ca. 9% GC yield) of the product resulting from the 1,4-addition of the 2-thienyl group was observed. This tendency was even more pronounced when the reaction was carried out in the presence of boron trifluoride etherate. In this reaction, 1,4-addition of the 2-thienyl group was the major product (59% GC yield) along with the usual 1,4-adduct (ca. 10% GC yield) (entries 3 and 4, Table III).

3. Reactions of RZnX with Allylic Halides. Since the allyl moiety is an integral feature of many natural products and biosynthetic intermediates, allylic compounds have been of considerable synthetic importance. Substitution reactions of allylic halides with organometallic reagents have provided an important route for the synthesis of these allylic compounds. Many factors affect the regiochemistry of these reactions, including the nature of the leaving group,[20] the degree of substitution at the two ends of the allylic system,[21] the solvent system,[22] the nature of the nucleophile and the catalyst.[22] In general, substitution of allylic substrates with or without complete allylic rearrangement is still an unpredictable process. While considerable research has been done on the coupling reactions of allylic halides with a variety of organometallic reagents, in only a few instances were the desired results obtained. Miyaura[23] et al. have found that $[(C_3H_7)_3BC-H_3]Cu$ reacted with cinnamyl chloride in THF to give a 96% yield of exclusively the γ-product (S_N2'). However, this is the only example reported with 100% allylic rearrangement. Mouric and Pabon[24] indicated that when greater than 1.5 equiv of *n*-butyl- or vinyllithium cuprate/dimethyl sulfide complex was treated with 1-chloro-2-butene at −76 °C in diethyl ether, almost negligible allylic rearrangement was seen. Yoshida[25] et al. synthesized the unsaturated ester via the CuCN-catalyzed allylation of zinc esters in THF/DMA at 60 °C. Although the yields were high, the regioselectivity was poor [S_N2:S_N2' = (15–28):(85–72)]. Nakamura[26] et al. stated that allylation of organozinc reagents in the presence of 5 mol % $CuBr\cdot Me_2S$ catalyst took place in a highly S_N2'-selective manner, whereas in the presence of a nickel catalyst excellent S_N2 selectivity was obtained. However, in the S_N2'-selective allylation reactions only simple alkylzinc compounds (methyl to butyl) were used and in the S_N2 selective allylation reactions only primary allylic chlorides were used and surprisingly, no homocoupling occurred. Probably, the most successful regioselective allylation of γ-attack of allylic halides was reported by Yamamoto.[27] He found that $RCu\cdot BF_3$ attacked at the γ-position of the allylic substrate irrespective of the degree of substitution at the two ends of the allylic system (84–99.7%). We have been able to carry out the highly regioselective γ-alkylation of allylic halides using highly functionalized organozinc compounds mediated by CuCN·2LiBr at 0 °C. Not only are the additions highly regioselective, but the organozinc reagents can also be highly functionalized. Both alkylzinc halides and arylzinc halides react with 3-chloro-1-butene to give 100% γ-attack (S_N2') (entries 5 and 7, Table IV). Alkylzinc halides react with crotyl chloride and cinnamyl chloride to give about 97% of the S_N2' products (entries

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(16) Petrier, C.; Dupuy, C.; Luche, J. L. *Tetrahedron Lett.* **1986**, *27*, 3149.
(17) Isobe, M.; Kondo, S.; Nagasawa, N.; Goto, T. *Chem. Lett.* **1977**, 679.
(18) Watson, R. A.; Kjonaas, R. A. *Tetrahedron Lett.* **1986**, *27*, 1437.
(19) Lipshutz, B. H.; Parker, D. A; Nguyen, S. L.; McCarthy, K. E.; Barton, J. C.; Whitney, S. E.; Kotsuki, H. *Tetrahedron* **1986**, *42*, 2873.
(20) For example, allylic alcohols, allylic esters, allylic halides, and allylic tosylates.
(21) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901 and reference cited therein.
(22) See examples in ref 24 and ref 26.
(23) Miyaura, N.; Itoh, M.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2199.
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(25) Ochiai, H.; Tamaru, Y.; Tsubaki, K.; Yoshida, Z. *J. Org. Chem.* **1987**, *52*, 4418.
(26) (a) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, J. *J. Am. Chem. Soc.* **1987**, *109*, 8056. (b) Sekiya, K.; Nakamura, E. *Tetrahedron Lett.* **1988**, 5155.
(27) Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 2318 and references cited therein.

1–3 and 8–10, Table IV). Even 1-bromo-3-methyl-2-butene, with the highly hindered γ-position, yields up to 95% of S_N2' products (entries 11–13, Table IV). The arylzinc halide reacts with crotyl chloride to give up to 80% of the S_N2' product. Temperature did not seem to affect the regioselectivity of attack of the alkyl or aryl zinc halides. Reactions run at −78 °C for about 10 min and then gradually warmed to room temperature had almost the same regioselectivity as the reaction run at 0 °C.

4. Reactions of RZnX with Aryl or Vinyl Halides. Negishi[28] and co-workers have shown that organozinc compounds can be readily cross-coupled with aryl and vinyl halides using a palladium catalyst. As their organozinc compounds were prepared by a metathesis reaction from the corresponding organolithium reagent, limited functionality could be tolerated. The highly functionalized organozinc compounds, prepared from highly reactive zinc, were found to cross-couple readily with aryl and vinyl halides when catalyzed by tetrakis(triphenylphosphine)-palladium ($Pd(PPh_3)_4$). The reaction proceeds in excellent yields, producing highly functionalized symmetrical and unsymmetrical biaryls, and symmetrical and unsymmetricaly butadienes (Table V). Attempts to cross-couple alkyl or aryl zinc reagents with 1,2-dibromobenzene failed. Similarly the 1,4-dibromozinc butane reagent prepared from 1,4-dibromobutane also failed to undergo a cyclizational reaction with 1,2-dibromobenzene.

Conclusions

Highly reactive zinc prepared by the lithium naphthalenide reduction of $ZnCl_2$ readily undergoes oxidative addition to highly functionalized alkyl, aryl, and vinyl halides under mild conditions to generate the corresponding organozinc compounds in excellent yields. These organozinc compounds mediated by Cu(I) salts cross-couple with acid chlorides, conjugatively add to α,β-unsaturated ketones, and regioselectivity undergo S_N2' substitution reactions with allylic halides. They also cross-couple with aryl or vinyl halides with Pd(0) catalysts. The yields are good to excellent. Accordingly, this approach considerably increases the synthetic potential of organozinc intermediates.

Experimental Section

General Information. Melting points are uncorrected. ^1H NMR ($CDCl_3$) spectra were recorded on a 200- or a 360-MHz NMR spectrometer. ^{13}C NMR spectra were recorded on a 50-MHz spectrometer. Analytical gas chromatography analysis was done using stainless steel columns or using a "megabore" glass capillary column. Stainless steel columns ($^1/_8$ in. diameter) were typically packed with silicon OV-17 (3%) on Chromosorb W-AW (100–120 mesh) with column lengths varying from 10 to 15 ft.

Reactions were carried out on a dual manifold vacuum/argon system. The Linde prepurified grade argon was further purified by passing it through a 150 °C catalyst column (BASF R3-11) and then through a column of phosphorus pentoxide, followed by a column of granular potassium hydroxide. The handling of air-sensitive materials was performed, whenever possible, under argon in a Vacuum Atmospheres Company drybox. Chemical reagents were primarily purchased from commercial sources and were used as received. Anhydrous $ZnCl_2$, $ZnBr_2$, and ZnI_2 were purchased from Cerac, Inc., and were typically stored in the drybox and used as received. THF and DME were freshly distilled before use from sodium/potassium alloy under a purified argon atmosphere.

(1) Typical Preparation of Active Zinc. Two 50-mL two-necked flasks, A and B, were equipped with rubber septa, condensers topped with argon inlets, and Teflon-coated magnetic stir bars. Flask A was charged with freshly cut lithium (0.213 g, 30.63 mmol) and naphthalene (3.987 g, 31.15 mmol). Flask B was charged with anhydrous $ZnCl_2$ (2.09 g, 15.37 mmol). Both of these operations were performed in the argon atmosphere drybox. The flasks were then transferred to the manifold system and the argon inlet fitted. Freshly distilled THF (15 mL) was added to both flasks A and B via a syringe, and the mixtures were stirred at room temperature. The solution in flask A changed from colorless to dark green almost immediately. The lithium was consumed in about 2 h, and the $ZnCl_2$ solution was transferred dropwise to the flask A by a cannula over 15 min. The active zinc was typically used at this point, but it can be washed several times with fresh solvent if naphthalene presents a problem with product isolation or if the solvent needs to be changed.

(2) Typical Generation of Organozinc Halides from Organic Halides and Active Zinc and Their Copper-Mediated Coupling with Acid Chlorides. Ethyl 4-iodobenzoate (1.934 g, 7.00 mmol) was added neat, via a syringe, to the active zinc (15.40 mmol) at room temperature. The reaction mixture was stirred for 3 h at room temperature. The solution was allowed to stand for about 3 h to allow the excess zinc to settle from the dark brown organozinc iodide solution. The top solution was then transferred carefully via a cannula to another two-necked flask under an argon atmosphere and cooled to −20 °C. A solution prepared by mixing CuCN (0.651 g, 7.27 mmol) and anhydrous LiBr (1.273 g, 14.66 mmol) in THF (10 mL) was added at −20 °C. The reaction mixture was gradually warmed to 0 °C and stirred at 0 °C for about 15 min. The solution was then cooled to −25 °C, and valeryl chloride (0.851 g, 7.02 mmol) was added neat via a syringe. The mixture was then worked up by pouring into a saturated NH_4Cl aqueous solution (20 mL) and extracting with diethyl ether (3 × 20 mL). The combined organic layers were dried over anhydrous $CaCl_2$. The resultant crude product was chromatographed on flash silica gel using gradient elution (hexanes to remove naphthalene first, then hexanes/ethyl acetate) to give ethyl 4-(1-oxopentyl)benzoate (1.360 g, 5.81 mmol) as a white crystalline solid in 83% isolated yield: mp 47.5–48.0 °C; ^1H NMR (360 MHz) 7.97–8.20 (m, 4 H), 4.38 (q, J = 7.1 Hz, 2 H), 3.00 (t, J = 7.3 Hz, 2 H), 1.66–1.77 (m, 2 H), 1.42 (t, J = 7.1 Hz, 3 H), 1.37–1.48 (m, 2 H), 0.96 (t, J = 7.2 Hz, 3 H); ^{13}C NMR 199.7, 165.6, 140.1, 133.9, 129.6, 127.7, 61.2, 38.5, 26.1, 22.3, 14.1, 13.8; IR (CCl_4) 3040, 2960, 1724, 1694, 1503 cm^{-1}; Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.94; H, 7.80.

1-Phenyl-1-nonanone: ref 29.

1-Oxo-1-phenyloctanenitrile:[29] mp 41.5–42.0 °C; ^1H NMR (360 MHz) 7.41–7.90 (m, 5 H), 2.96 (t, J = 7.2 Hz, 2 H), 2.32 (t, J = 7.1 Hz, 2 H), 1.73 (m, 2 H), 1.64 (m, 2 H), 1.35–1.52 (m, 4 H); ^{13}C NMR 199.8, 136.8, 132.7, 128.4, 127.7, 119.5, 38.0, 28.2, 28.1, 24.9, 23.6, 16.8; IR (CCl_4) 3061, 2938, 2245, 1690, 1598 cm^{-1}.

7-Chloro-1-phenyl-1-heptanone: ref 29.

1,3-Diphenyl-1-propanone: ref 30.

Ethyl 5-oxononanoate:[31] ^1H NMR (200 MHz) 4.13 (q, J = 7.2 Hz, 2 H), 2.48 (t, J = 7.2 Hz, 2 H), 2.25–2.55 (m, 6 H), 1.85–1.93 (m, 2 H), 1.51–1.59 (m, 2 H), 1.25–1.40 (m, 2 H), 1.26 (t, J = 7.1 Hz, 3 H), 0.90 (t, J = 7.2 Hz, 3 H); ^{13}C NMR 210.3, 173.1, 60.2, 42.5, 41.4, 33.2, 25.8, 22.2, 18.8, 14.1, 13.7; IR (neat) 2958, 1736, 1714, 786 cm^{-1}.

Ethyl 5-oxo-5-phenylpentanoate: ref 32.

1-(*p*-Methylphenyl)-1-pentanone: ref 33.

1-(*p*-Chlorophenyl)-1-pentanone: ref 34.

Ethyl *p*-benzoylbenzoate: ref 29.

Ethyl *m*-benzoylbenzoate: ref 35.

Ethyl *o*-benzoylbenzoate: ref 36.

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(35) Spectral data match the Sadtler standard spectra, IR 15511; ^1H NMR 6780.

Ethyl *o*-(1-oxopentyl)benzoate: ^{1}H NMR (200 MHz) 7.30–7.95 (m, 4 H), 4.34 (q, J = 7.2 Hz, 2 H), 2.81 (t, J = 7.5 Hz, 2 H), 1.64–1.75 (m, 2 H), 1.31–1.52 (m, 2 H), 1.35 (t, J = 7.1 Hz, 3 H), 0.93 (t, J = 7.3 Hz, 3 H); ^{13}C NMR 205.4, 166.5, 143.0, 131.7, 129.6, 129.4, 128.7, 126.0, 61.3, 42.3, 25.9, 22.1, 13.8, 13.6; IR 2958, 2960, 1718, 1597, 1277, 760 cm^{-1}; Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.62; H, 7.97.

1-(*p*-Cyanophenyl)-1-pentanone: ref 37.

(*p*-Cyanophenyl)phenylmethanone: ref 38.

(*o*-Cyanophenyl)phenylmethanone: ref 29.

1-(*o*-Cyanophenyl)-1-pentanone: ref 37.

1-(*p*-Acetylphenyl)-1-pentanone: ref 37.

***trans*-1-Phenylhept-1-en-3-one**:[39] mp 32.0–32.5 °C; ^{1}H NMR (360 MHz) 7.35–7.59 (m, 6 H), 6.75 (d, J = 16.2 Hz, 1 H), 2.66 (t, J = 7.5 Hz, 2 H), 1.60–1.68 (m, 2 H), 1.35–1.45 (m, 2 H), 0.94 (t, J = 7.3 Hz, 3 H); ^{13}C NMR 200.6, 142.3, 134.6, 130.3, 128.9, 128.2, 126.3, 40.6, 26.5, 22.4, 13.9; IR (CCl_4) 3029, 2960, 1695, 1670, 1612, 1577, 1450 cm^{-1}.

1,2-Diphenylethanone:[40] mp 58–59 °C; ^{1}H NMR (200 MHz) 7.20–8.15 (m, 10 H), 4.27 (s, 2 H); ^{13}C NMR 197.5, 136.6, 134.5, 133.1, 129.4, 129.4, 128.6, 128.6, 126.8, 45.4; IR (CCl_4) 3066, 3030, 2958, 1685, 1600, 1274 cm^{-1}.

1,6-Diphenyl-1,6-hexanedione:[41] mp 103.5–104.5 °C; ^{1}H NMR 7.42–8.00 (m, 10 H), 2.95–3.08 (m, 4 H), 1.80–1.90 (m, 4 H); ^{13}C NMR 200.0, 136.9, 132.9, 128.5, 128.0, 38.4, 23.9; IR (CCl_4) 2937, 1691, 1598, 1581, 1448, 1459, 1267, 958 cm^{-1}.

1,4-Diacetylbenzene: ref 42.

(3) Typical Copper-Mediated Conjugate Addition Reaction of Organozinc Halides to α,β-Unsaturated Ketones. Ethyl 4-bromobutanoate (0.705 g, 3.62 mmol) was added neat, via syringe, to the active zinc (4.00 mmol) at room temperature. The reaction mixture was stirred at room temperature for 18 h, giving a dark solution of the alkylzinc bromide species. A solution prepared by mixing CuCN (0.327 g, 3.65 mmol) and anhydrous LiBr (0.636 g, 7.32 mmol) in THF (10 mL) was added at 0 °C. The reaction mixture was stirred at 0 °C for 15 min and then cooled to −78 °C. $(CH_3)_3SiCl$ (0.719 g, 6.62 mmol) and $BF_3{\cdot}Et_2O$ (0.800 g, 5.64 mmol) were added neat via a syringe, and the solution was stirred for 10–15 min. A solution of 2-cyclohexenone (0.269 g, 2.80 mmol) in THF (10 mL) was added dropwise over 20 min to the reaction mixture at −78 °C. The reaction mixture was stirred at −78 °C for 3 h and slowly warmed to 0 °C. After being stirred at 0 °C for 1–2 h, the reaction mixture was then worked up and purified by a similar procedure to that described in the Experimental Section (2) to give 3-(3-carbethoxypropyl)-cyclohexanone (0.442 g) as an oil in 74% yield (92% GC yield): ^{1}H NMR (200 MHz) 4.13 (q, J = 7.2 Hz, 2 H), 1.26–2.50 (m, 15 H including 2.29 (t, J = 7.2 Hz)), 1.26 (t, J = 7.2 Hz, 2 H); ^{13}C NMR 211.1, 173.0, 60.0, 47.7, 41.2, 38.5, 35.6, 34.0, 30.8, 24.9, 21.8, 14.0; IR (neat) 2940, 1740, 1720, 1455, 1420, cm^{-1}; HREI calcd for $C_{12}H_{20}O_3$ m/e 212.1413, found 212.1411.

11-Chloro-5-methyl-3-undecanone: ^{1}H NMR (200 MHz) 3.53 (t, J = 6.7 Hz, 2 H), 2.14–2.48 (m, 4 H including 2.40 (q, J = 7.2 Hz, 3 H), 1.87–2.12 (m, 1 H), 1.66–1.85 (m, 2 H), 1.08–1.53 (m, 8 H), 1.04 (t, J = 7.3 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 3 H); ^{13}C NMR 221.5, 49.8, 45.0, 36.7, 36.4, 32.5, 29.2, 28.9, 26.8, 26.7, 19.8, 7.7; IR (neat) 2965, 2940, 2860, 1715, 1465, 1415, 720 cm^{-1}; HREI calcd for $C_{12}H_{23}{}^{35}ClO$ m/e 218.1437, found m/e 218.1432; calcd for $C_{12}H_{23}{}^{37}ClO$ m/e 220.1408, found m/e 220.1405.

3-Cyclohexylcyclohexanone:[13] ^{1}H NMR (200 MHz) 0.84–2.47 (m); ^{13}C NMR 212.7, 45.5, 44.6, 42.7, 41.6, 29.9, 29.8, 28.4, 26.5, 25.6; IR (neat) 2930, 2855, 1715, 1450, 1430, cm^{-1}; HREI calcd for $C_{12}H_{20}O$ m/e 180.1514, found m/e 180.1515.

3-(4-Carbethoxyphenyl)cyclohexanone: ^{1}H NMR (200 MHz) 7.96–8.07 (m, 2 H), 7.24–7.37 (m, 2 H), 4.37 (q, J = 7.1 Hz, 2 H), 2.97–3.18 (m, 1 H), 2.28–2.68 (m, 4 H), 1.66–2.26 (m, 4 H), 1.39 (t, J = 7.2 Hz, 3 H); ^{13}C NMR 210,01, 166.2, 149.2, 129.9, 128.9, 126.5, 60.8, 48.3, 44.5, 41.0, 32.3, 25.3, 14.2; IR (KBr) 3045, 2940, 1710 (br), 1610, 1445, 1420, 850 cm^{-1}; HREI calcd for $C_{15}H_{18}O_3$ m/e 246.1256, found 246.1255.

(4) Typical Reaction of Organozinc Halides with Allylic Halides. A solution prepared by mixing CuCN (0.495 g, 5.53 mmol) and anhydrous LiBr (0.965 g, 11.11 mmol) in THF (10 mL) under an argon atmosphere was precooled to −20 °C and added to (6-cyanohexyl)zinc bromide (5.46 mmol, in about 10 mL of THF) at −20 °C, and the mixture was then slowly warmed to 0 °C. 1-Chloro-2-butene (0.544 g, 6.01 mmol, 1.1 equiv) was added neat, via a syringe. The reaction mixture was stirred at this temperature for about 30 min. The reaction mixture was worked up and purified by a similar procedure to that described in the Experimental Section (2) to give a 91% yield of S_N2' and S_N2 mixture. The ratio determined by the ^{1}H NMR spectroscopy was $S_N2':S_N2$ = 97:3. 8'Methyldec-9-enenitrile (major product): ^{1}H NMR (360 MHz) 5.62–5.72 (m, 1 H), 4.87–4.97 (m, 2 H), 2.33 (t, J = 7.1 Hz, 2 H), 2.07–2.12 (m, 1 H), 1.60–1.71 (m, 2 H), 1.23–1.35 (br s, 6 H), 0.97 (d, J = 6.7 Hz, 3 H); ^{13}C NMR 144.5, 119.6, 112.3, 37.6, 36.3, 28.7, 28.5, 26.7, 25.2, 20.1, 16.2; IR (neat) 3014, 2928, 2856, 2246, 966. Anal. Calcd for $C_{11}H_{19}N$: C, 79.94; H, 11.59; N, 8.47. Found: C, 79.63; H, 11.81; N, 8.47.

Ethyl 5-methylhept-6-enoate:[25] ^{1}H NMR (360 MHz) 5.62–5.72 (m, 1 H), 4.90–4.99 (m, 2 H), 4.12 (q, J = 7.1 Hz, 2 H), 2.76 (t, J = 7.5 Hz, 2 H), 2.08–2.21 (m, 2 H), 1.48–1.71 (m, 2 H), 1.22–1.40 (m, 2 H), 1.25 (t, J = 7.1 Hz, 3 H), 0.99 (d, J = 6.7 Hz, 3 H); ^{13}C NMR 173.5, 144.1, 112.7, 60.0, 37.5, 35.7, 34.3, 22.6, 20.0, 14.1; IR (neat) 3077, 2960, 1739, 1640, 995, 912 cm^{-1}; HREI calcd for $C_{10}H_{18}O_2$ m/e 170.1307, found 170.1301.

9-Chloro-3-methylnon-1-ene: ^{1}H NMR 5.60–5.73 (m, 1 H), 4.88–4.97 (m, 2 H), 3.53 (t, J = 7.1 Hz, 2 H), 2.06–2.13 (m, 1 H), 1.72–1.80 (m, 2 H), 1.38–1.45 (m, 2 H), 1.25–1.31 (m, 6 H), 0.98 (d, J = 6.7 Hz, 3 H); ^{13}C NMR 144.8, 112.3, 45.1, 37.7, 36.5, 32.6, 29.0, 27.2, 26.9, 20.2; IR (neat) 3068, 3052, 2929, 1639, 910, 785; HREI calcd for $C_{10}H_{19}Cl$ m/e 174.1177, found 174.1178. Anal. Calcd for $C_{10}H_{19}Cl$: C, 68.75; H, 10.96. Found: C, 68.36; H, 10.67.

Ethyl 4-(1-methyl-2-propenyl)benzoate: ^{1}H NMR (360 MHz) 7.21–8.02 (m, 4 H), 5.90–6.02 (m, 1 H), 5.01–5.11 (m, 2 H), 4.36 (q, J = 7.1 Hz, 2 H), 3.43–3.58 (m, 1 H), 1.38 (t, J = 7.2 Hz, 6 H); ^{13}C NMR 166.5, 150.8, 142.3, 129.7, 129.0, 127.2, 113.8, 60.7, 43.1, 20.5, 14.3; IR (neat) 2978, 1726, 1610, 1587, 1415, 1392, 1367, 916, 584 cm^{-1}; HREI calcd for $C_{13}H_{16}O_2$ m/e 204.1151, found 204.1146.

Ethyl oct-6-enoate: ref 25.

Undec-9-enenitrile: ^{1}H NMR (360 MHz) (cis and trans mixture) 5.35–5.45 (m, 2 H), 2.33 (t, J = 7.1 Hz, 2 H), 1.93–2.14 (m, 2 H), 1.6–1.7 (m, 5 H), 1.3–1.5 (m, 2 H), 1.2–1.45 (m, 6 H), ^{13}C NMR 131.2 (trans), 130.4 (cis), 124.6 (trans), 123.6 (cis), 120.0, 32.3, 29.3, 29.2, 28.7, 26.5, 25.2, 17.7, 16.9; IR (neat) 2927, 2856, 2247, 2463, 966 cm^{-1}. Anal. Calcd for $C_{11}H_{19}N$: C, 79.94; H, 11.59; N, 8.47. Found: C, 79.80; H, 11.46; N, 8.15.

Ethyl *p*-2-butenylbenzoate (cis and trans mixture, trans is the major product): ^{1}H NMR (200 MHz) 1.38 (t, J = 7.1 Hz, 3 H), 1.69 (d, J = 4.75 Hz, 3 H, trans) 1.69 (d, J = 1.07 Hz, 3 H, cis), 3.35 (d, J = 4.61 Hz, 2 H, trans), 3.45 (d, J = 6.2 Hz, 2 H, cis), 4.36 (q, J = 7.13 Hz, 2 H), 5.53–5.58 (m, 2 H), 7.21–7.98 (m, 4 H); ^{13}C NMR 166.6, 146.5, 146.4, 129.7, 129.6, 129.0, 128.4, 128.2. 128.2, 128.0, 127.1, 125.6, 77.64, 77.01, 76.37, 60.70, 39.0 (trans), 33.12 (cis), 17.8 (trans), 14.3, 12.8 (cis); IR (neat) 3023, 2856, 1716, 1610, 701, 761 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.28; H, 7.81.

Ethyl 5-phenylhept-6-enoate: ^{1}H NMR (360 MHz) 7.15–7.30 (m, 5 H), 5.88–6.08 (m, 1 H), 4.06–4.14 (m, 2 H), 4.10 (q, J = 7.1 Hz, 2 H), 3.21–3.27 (m, 1 H), 2.28 (t, J = 7.3 Hz, 1 H), 1.45–1.80 (m, 4 H), 1.23 (t, J = 7.1 Hz, 3 H); ^{13}C NMR 173.4, 143.9, 141.8, 128.4, 127.5, 126.2, 114.2, 60.1, 49.6, 34.7, 34.1, 22.9, 14.2; IR (neat) 3081, 2979, 1735, 761, 701 cm^{-1}; HREI calcd for $C_{15}H_{20}O_2$ m/e 232.1464, found 232.1461. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.04; H, 8.68.

8-Phenyldec-9-enenitrile: ^{1}H NMR (360 MHz) 7.12–7.32 (m, 5 H), 5.80–6.00 (m, 1 H), 5.0–5.04 (m, 2 H), 3.22 (q, J = 7.5 Hz, 1 H), 2.27 (t, J = 7.1 Hz, 2 H), 1.63–1.73 (m, 2 H), 1.55–1.62 (m,

(36) Spectral data match the Sadtler standard spectra, IR 5157; ^{1}H NMR 6780; ^{13}C NMR 8626.

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(40) (a) Allen, C. F. H.; Barker, W. E. *Org. Synth.* **1932**, *12*, 16. (b) Spectra match the spectrum of Aldrich for this compound, FT-IR 1(2) 11C; NMR 2(2) 12 C.

(41) (a) Cahiez, G.; Bernard, D.; Normant, J. F. *Synthesis* **1977**, 130. (b) Spectra match the Sadtler standard spectra, ^{1}H 2155; IR 8964.

(42) The spectral data match the Aldrich spectra data: NMR 2(2), 17C; FT-IR 1(2) 17A.

2 H), 1.18–1.25 (m, 6 H); ^{13}C NMR 144.3, 142.2, 128.3, 127.4, 126.1, 119.7, 113.9, 49.8, 35.2, 28.6, 28.4, 27.1, 25.2, 16.9; IR (neat) 3081, 3027, 2930, 2857, 2246, 1636, 1601, 1493, 1452 cm^{-1}. Anal. Calcd for $C_{16}H_{21}N$: C, 84.53; H, 9.31; N, 6.16. Found: C, 84.27; H, 9.49; N, 6.07.

3,5-Diphenyl-1-pentene:[43] ^{1}H NMR (360 MHz) 7.10–7.32 (m, 10 H), 5.91–6.00 (m, 1 H), 5.00–5.05 (m, 2 H), 3.26 (m, 1 H), 2.47–2.67 (m, 2 H), 1.99–2.06 (m, 2 H); ^{13}C NMR 144.1, 142.2, 142.1, 128.5, 128.4, 128.3, 127.6, 126.2, 125.7, 114.3, 49.3, 37.0, 33.7.

Ethyl 5,5-Dimethylhept-6-enoate: ref 25.

8,8-Dimethyldec-9-enenitrile: ^{1}H NMR (360 MHz) 5.70–5.78 (m, 1 H), 4.85–4.91 (m, 2 H), 2.33 (t, J = 7.1 Hz, 2 H), 1.60–1.68 (m, 4 H), 1.40–1.48 (m, 2 H), 1.19–1.34 (m, 8 H), 0.97 (s, 6 H); ^{13}C NMR 148.4, 124.6, 119.7, 110.1, 42.5, 29.4, 28.6, 26.6, 25.3, 24.2, 17.0; IR (neat) 2958, 2931, 2859, 2247, 1639, 1464, 1004, 910 cm^{-1}. Anal. Calcd for $C_{12}H_{21}N$: C, 80.38; H, 11.80; N, 7.81. Found: C, 80.02; H, 11.98; N, 7.71.

3,3-Dimethyl-5-phenylpent-1-ene:[44] ^{1}H NMR (360 MHz) 7.13–7.28 (m, 5 H), 5.78–5.87 (m, 1 H), 4.94–4.99 (m, 2 H), 2.48–2.54 (m, 2 H), 1.05 (s, 6 H); ^{13}C NMR 148.1, 143.3, 128.3, 125.5, 110.7, 44.9, 36.7, 31.2, 26.7; IR (neat) 3086, 2960, 2929; 1641, 1604, 1496, 1454, 910 cm^{-1}.

(5) Typical Procedure for the Reaction of RZnX with Aryl and Vinyl Halides. (4-Carbethoxyphenyl)zinc iodide (2.16 mmol, in about 10 mL of THF) was transferred via a cannula to a THF solution of 5 mol % $Pd(PPh_3)_4$ (0.127 g, 0.11 mmol) and 4-bromobenzonitrile (0.400 g, 2.19 mmol) at room temperature under an argon atmosphere. The solution was then stirred for 3 h. The reaction, worked up by a similar procedure to that described in the Experimental Section (2), yields ethyl 4-(4-cyanophenyl)-benzoate (0.433 g, 1.73 mmol) in 80% as a crystalline solid: mp 114–115 °C; ^{1}H NMR (360 MHz) 7.60–8.21 (m, 8 H), 4.42 (q, J = 7.1 Hz, 2 H), 1.42 (t, J = 7.1 Hz, 3 H); ^{13}C NMR 165.9, 144.2, 143.1, 132.5, 130.4, 130.1, 127.7, 127.0, 118.5, 111.6, 61.0, 14.2; IR (CCl_4) 2981, 2231, 1722, 1608, 1276, 1109 cm^{-1}; HREI calcd for $C_{16}H_{13}NO_2$ m/e 251.0947, found 251.0949. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.25; H, 5.17; N, 5.31.

Ethyl 4-(4-acetylphenyl)butanoate:[45] ^{1}H NMR (360 MHz) 7.30–7.91 (m, 4 H), 4.13 (q, J = 7.1 Hz, 2 H), 2.71 (t, J = 7.6 Hz, 2 H), 2.58 (s, 3 H), 2.32 (t, J = 7.40 Hz, 3 H), 1.91–2.02 (m, 2 H), 1.25 (t, J = 7.1 Hz, 3 H); ^{13}C NMR 197.6, 173.1, 147.2, 135.2, 128.6, 128.5, 60.3, 35.0, 33.5, 26.4, 26.1, 14.2; IR (neat) 2979, 2937, 1732, 1684, 1606, 845, 815 cm^{-1}; HREI calcd for $C_{14}H_{18}O_3$ m/e 234.1256, found 234.1257. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.21; H, 7.62.

Ethyl 4-(4-cyanophenyl)butanoate: ^{1}H NMR (360 MHz) 7.31–7.62 (m, 4 H), 4.13 (q, J = 7.2 Hz, 2 H), 2.73 (t, J = 7.7 Hz, 2 H), 2.33 (t, J = 7.3 Hz, 2 H), 1.92–2.01 (m, 2 H), 1.26 (t, J = 7.2 Hz, 3 H); ^{13}C NMR 172.7, 146.9, 131.9, 129.0, 118.7, 109.6, 60.1, 34.8, 33.1, 25.7, 13.9; IR (neat) 2979, 2937, 2227, 1732, 1606, 844, 817 cm^{-1}. Anal. Calcd for $C_{13}H_{15}O_2N$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.25; H, 7.05; N, 6.30.

Ethyl 4-(4-nitrophenyl)butanoate:[46] ^{1}H NMR (360 MHz) 7.34–8.16 (m, 4 H), 4.14 (q, J = 7.2 Hz, 2 H), 2.77 (t, J = 7.7 Hz, 2 H), 2.35 (t, J = 7.3 Hz, 2 H), 1.90–2.04 (m, 2 H), 1.26 (t, J = 7.1 Hz, 3 H); ^{13}C NMR 172.7, 149.2, 146.2, 129.1, 123.4, 60.1, 34.7, 33.1, 25.8, 14.0; IR (neat) 2981, 2938, 1732, 1604, 1598, 1520, 1346, 850, 746, 698 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.63; H, 6.42; N, 5.70.

4,4′-Dicarbethoxybiphenyl: ref 47.

Ethyl 3-(4-cyanophenyl)benzoate: mp 91.5–92.0 °C; ^{1}H NMR 7.52–8.34 (m, 8 H), 4.46 (q, J = 7.2 Hz, 2 H), 1.43 (t, J = 7.1 Hz, 3 H); ^{13}C NMR 166.1, 144.5, 139.3, 132.6, 131.4, 131.3, 129.6, 129.1, 128.2, 127.7, 118.7, 111.4, 61.2, 14.3; IR (CCl_4) 3020, 2981, 2400, 2231, 1716, 1608, 1309, 1247, cm^{-1}; HREI calcd for $C_{16}H_{13}NO_2$ m/e 251.0947, found 251.0949. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.68; H, 5.36; N, 5.42.

4,4′-Dicyanobiphenyl: ref 48.

Ethyl 3-(2-cyanophenyl)benzoate: mp 81.5–82.0 °C; ^{1}H NMR (200 MHz) 7.40–8.25 (m, 8 H), 4.41 (q, J = 7.1 Hz, 2 H), 1.41 (t, J = 7.1 Hz, 3 H); ^{13}C NMR 166.0, 144.4, 138.3, 133.7, 132.9, 132.9, 131.1, 130.0, 129.8, 129.7, 128.7, 127.9, 118.3, 111.3, 61.2, 14.3; IR (CCl_4) 3020, 2983, 2401, 2227, 1716, 1475, 1444, 1427, 1369, 1311, 1277, 1240, 930 cm^{-1}. Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.42; H, 5.18; N, 5.26.

2-Phenyl-1,3-butadiene: ref 49.

2-Methyl-3-phenyl-1,3-butadiene: ref 50.

Ethyl 2-(1,3-butadienyl)benzoate: ^{1}H NMR (200 MHz) 7.25–7.90 (m, 5 H), 6.47–6.78 (m, 2 H), 5.18–5.40 (m, 2 H), 4.37 (q, J = 7.1 Hz, 2 H), 1.40 (t, J = 7.1 Hz, 3 H); ^{13}C NMR 167.5, 138.6, 137.4, 132.2, 131.8, 131.2, 130.4, 129.0, 127.1, 126.7, 118.3, 61.0, 14.3; IR (neat) 2979, 1716, 1598, 1477, 1446, 1128, 1074, 1004, 754, 708; HREI calcd for $C_{13}H_{14}O_2$ m/e 202.0994, found 202.0992.

Ethyl 2-(3-methyl-1,3-butadienyl)benzoate: ^{1}H NMR (200 MHz) 7.26–7.92 (m, 4 H), 6.77 (d, J = 16.0 Hz, 1 H), 5.10–5.13 (m, 2 H), 4.38 (q, J = 7.1 Hz, 2 H), 2.01 (s, 3 H), 1.41 (t, J = 7.0 Hz, 3 H); ^{13}C NMR 167.6, 142.4, 139.0, 134.2, 131.9, 130.6, 128.9, 127.5, 126.9, 126.8, 117.8, 61.0, 18.7, 14.3; IR (neat) 3081, 1716, 1602, 1479, 1450, 1290, 1269, 1242, 964, 754, 710; HREI calcd for $C_{14}H_{16}O_2$ m/e 216.1151, found 216.1150.

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Registry No. I, 930-68-7; II, 100315-21-7; III, 71777-97-4; IV, 2497-21-4; $Br(CH_2)_6Cl$, 6294-17-3; $Br(CH_2)_7CH_3$, 111-83-1; $Br(CH_2)_3CO_2Et$, 2969-81-5; p-IC_6H_4Cl, 637-87-6; p-BrC_6H_4CN, 623-00-7; $Br(CH_2)_6CN$, 20965-27-9; p-$BrC_6H_4CO_2Et$, 5798-75-4; o-$BrC_6H_4CO_2Et$, 6091-64-1; m-$BrC_6H_4CO_2Et$, 24398-88-7; $Cl(CH_2)_3CO_2Et$, 3153-36-4; $Br(CH_2)_2Ph$, 103-63-9; p-BrC_6H_4Me, 106-38-7; p-$IC_6H_4CO_2Et$, 51934-41-9; o-BrC_6H_4CN, 2042-37-7; p-$BrC_6H_4COCH_3$, 99-90-1; (E)-PhCH=CHBr, 588-72-7; $PhCH_2Cl$, 100-44-7; $Br(CH_20_4Br$, 110-52-1; p-IC_6H_4I, 624-38-4; $BrZn(CH_2)_7CH_3$, 131379-13-0; p-$BrZnC_6H_4CN$, 131379-14-1; p-$BrZnC_6H_4CO_2Et$, 131379-15-2; p-$IZnC_6H_4CO_2Et$, 131379-16-3; o-$BrZnC_6H_4CN$, 131379-17-4; $ClZnC(=CH_2)Ph$, 119441-92-8; o-$BrZnCH=CHC_6H_4CO_2Et$, 131379-18-5; PhCOCl, 98-88-4; $CH_3(CH_2)_3COCl$, 638-29-9; CH_3COCl, 75-36-5; $ClCH_2CH=CHCH_3$, 591-97-9; $CH_3CH(Cl)CH=CH_2$, 563-52-0; $PhCH=CHCH_2Cl$, 2687-12-9; CH_3, 870-63-3; p-$BrC_6H_4NO_2$, 586-78-7; $BrCH=CH_2$, 593-60-2; $CH_3C(=CH_2)Br$, 557-93-7; $PhCO(CH_2)_7CH_3$, 6008-36-2; $PhCO(CH_2)_6CN$, 39755-15-2; $PhCO(CH_2)_6Cl$, 17734-41-7; $PhCO(CH_2)_2Ph$, 1083-30-3; $CH_3(CH_2)_3CO(CH_2)_3CO_2Et$, 24071-99-6; $PhCO(CH_2)_3CO_2Et$, 73172-56-2; $CH_3(CH_2)_3COC_6H_4$-p-Me, 1671-77-8; $CH_3(CH_2)_3COC_6H_4$-p-CO_2Et, 131379-19-6; $CH_3(CH_2)_3COC_6H_4$-p-Cl, 25017-08-7; $PhCOC_6H_4$-p-CO_2Et, 15165-27-2; $PhCOC_6H_4$-m-CO_2Et, 130339-72-9; $PhCOC_6H_4$-o-CO_2Et, 604-61-5; $CH_3(CH_2)_3COC_6H_4$-o-CO_2Et, 131379-20-9; $CH_3(CH_2)_3COC_6H_4$-p-CN, 30611-20-2; $PhCOC_6H_4$-p-CN, 1503-49-7; $PhCOC_6H_4$-o-CN, 37774-78-0; $CH_3(CH_2)_3COC_6H_4$-o-CN, 79784-55-7; $CH_3(CH_2)_3COC_6H_4$-p-$COCH_3$, 79784-59-1; (E)-$CH_3(CH_2)_3COCH=CHPh$, 41903-83-7; $PhCOCH_2Ph$, 451-40-1; $PhCO(CH_2)_4COPh$, 3375-38-0; $CH_3COC_6H_4$-p-$COCH_3$, 1009-61-6; $Cl(CH_2)_6CH(CH_3)CH_2COCH_2CH_3$, 131379-21-0; $H_2C=CHCH(CH_3)CH_2(CH_2)_2CO_2Et$, 109976-56-9; (E)-$H_3CCH=CH(CH_2)_4CO_2Et$, 101773-18-6; $H_2C=CHCH(CH_3)CH_2(CH_2)_5CN$, 131379-23-2; (Z)-$CH_3CH=CH(CH_2)_7CN$, 131379-24-3; $Cl(CH_2)_6CH(CH_3)CH=CH_2$, 131379-25-4; (E)-$CH_3CH=CH(CH_2)_7CN$, 131379-26-5; $H_2C=CHCH(CH_3)C_6H_4$-p-CO_2Et, 131379-27-6; (Z)-$CH_3CHCH_2C_6H_4$-p-CO_2Et, 131379-28-7; $H_2C=CHCH(Ph)CH_2$-

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$(CH_2)_2CO_2Et$, 131379-29-8; (*E*)-$CH_3CH{=}CHCH_2C_6H_4$-*p*-CO_2Et, 131379-30-1; $H_2C{=}CHCH(Ph)CH_2(CH_2)_5CN$, 131379-31-2; (*E*)-$CH_3CH{=}CH(CH_2)_4CO_2Et$, 61141-97-7; $H_2C{=}CHC(CH_3)(CH_3)CH_2(CH_2)_2CO_2Et$, 109976-59-2; $H_2C{=}CHC(CH_3)(CH_3)CH_2(CH_2)_5CN$, 131379-32-3; $H_2C{=}CHC(CH_3)(CH_3)CH_2CH_2Pgh$, 61142-18-5; *p*-$COCH_3C_6H_4(CH_2)_3CO_2Et$, 71665-59-3; *p*-$CNC_6H_4(CH_2)_3CO_2Et$, 131379-33-4; *p*-$NO_2C_6H_4(CH_2)_3CO_2Et$, 34153-33-8; *p*-$CNC_6H_4C_6H_4$-*p*-$CO_2Et$, 89409-89-2; *p*-$CO_2EtC_6H_4C_6H_4$-*p*-$CO_2Et$, 47230-38-6; *m*-$CO_2EtC_6H_4C_6H_4$-*p*-CN, 131379-34-5; *p*-$CNC_6H_4C_6H_4$-*p*-CN, 1591-30-6; *o*-$CNC_6H_4C_6H_4$-*m*-CO_2Et, 131379-35-6; $PhC(=CH_2)CH=CH_2$, 2288-18-8; $PhC(=CH_2)C(CH_3)=CH_2$, 18476-73-8; $H_2C{=}CHCH{=}CHC_6H_4$-*o*-CO_2Et, 131379-36-7; $H_2C{=}C(CH_3)CH{=}CHC_6H_4$-*o*-$CO_2Et$, 131379-37-8; *m*-$BrZnC_6HCO_2Et$, 131379-38-9; bromo[3-(ethoxycarbonyl)propyl-*C*,*O*]zinc, 131379-39-0; bromo[2-(ethoxycarbonyl)phenyl-*C*,*O*]zinc, 131379-40-3; chloro[3-(ethoxycarbonyl)propyl]-*C*,*O*]zinc, 131379-41-4; cyclohexyl bromide, 108-85-0; 3-cyclohexylcyclohexanone, 7122-93-2; 3-(4-carbethoxyphenyl)cyclohexanone, 131379-22-1; lithium 2-thienylcyanocuprate, 112426-02-5.

Supplementary Material Available: ^1H and ^{13}C NMR spectra and spectral data for the new title compounds (32 pages). Ordering information is given on any current masthead page.

The Generation and Rearrangement of 2-(Diazoacetyl)cyclobutanones: The Formation of 5-Spirocyclopropyl-2(5*H*)-furanones

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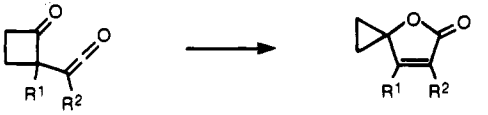
We describe here a simple synthesis of 2-(diazoacetyl)cyclobutanones and their facile thermal rearrangement to 5-spirocyclopropyl-$\Delta^{\alpha,\beta}$-butenolides. The yield of the rearrangement product is high, and the reaction is completely stereospecific. α-Ketenylcyclobutanones have been identified spectroscopically as intermediates, and their rearrangement was studied kinetically. A strained dipolar cyclic transition is proposed for the rearrangement of the α-ketenylcyclobutanones to the corresponding 5-spirocyclopropyl-$\Delta^{\alpha,\beta}$-butenolides.

Introduction

Strained ring compounds, long of interest to the organic chemist because of their curious chemical and spectroscopic properties,[1] have recently attracted the interest of the synthetic organic chemist due to the explosive development of synthetic routes to highly functionalized starting materials.[2] For no class of materials has this interest been more apparent than for the cyclobutanones[2e,f,3] where a virtual plethora of new synthetic routes have stimulated their use as synthetic intermediates. These materials also show, in addition to a vast variety of strain-driven ground-state reactions and rearrangements, a rich and varied photochemistry.[3,4]

We have been interested for some time in rearrangements of cyclobutanone derivatives.[5] This began with the discovery that a number of cyclobutanones underwent a variety of electrophilically initiated ring opening reactions in the presence of appropriate electrophile–nucleophile combinations. Our initial studies first utilized Lewis acid catalysts in the presence of compatible nucleophiles[5b,c] and evolved to reagents containing both reactants in a single molecule (e.g., trimethylsilyl iodide).[5d] In each case, regioselective ring opening of the cyclobutanone ring was observed with the formation of polyfunctionalized products. We were interested in determining whether appropriately masked electrophilic functionality tethered to a cyclobutanone ring could be selectively activated in the presence of the highly strained carbonyl functionality and utilized to initiate interesting intramolecular electrophilic rearrangements. In this regard, the electrophile after initiating the structural rearrangement should ideally be transformed into a nucleophilic reagent capable of terminating the reaction intramolecularly. In many cases, functional groups such as ketenes and isocyanates can play such a dual role.[6] It was envisioned that such reactants bonded appropriately to the α-position of a cyclobutanone derivative might promote the rearrangement shown below to generate a variety of interesting 5-spirocyclopropylbutenolides.



(1)

$\Delta^{\alpha,\beta}$-Butenolides are valuable synthetic reagents which constitute the active functionality of many known natural products, and many synthetic approaches to these materials have been developed and described.[7] Similarly, many

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