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Nickel-Catalyzed Arylative Ring-Opening of 3-Methylenecycloalkane-1,1-dicarboxylates

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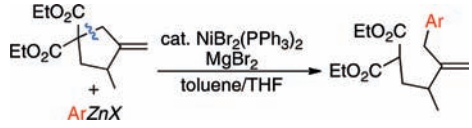
ABSTRACT



An arylative ring-opening reaction of cyclic allylmalonates with arylzinc reagents under nickel catalysis has been developed. Upon the ring-opening sp^3C-sp^3C bond cleavage, the allylic moiety serves as an allylic electrophile to react with arylzinc reagents. Simultaneously, the malonate moiety is converted to the corresponding zinc enolate, which can react further with electrophiles. The overall process increases molecular complexity and diversity starting from readily available substrates and is useful in organic synthesis.

Development of efficient methods for cleavage of C−C bonds catalyzed by transition-metal complexes is a new trend and a challenging topic of modern organic chemistry.[1,2] Having been long pursued, cleavage of unstrained sp^3C-sp^3C bonds is still difficult owing to their stability as well as the high directionality of the σ-orbital of sp^3C-sp^3C bonds. Several noteworthy examples of cleavage of unstrained sp^3C-sp^3C bonds under transition-metal catalysis have been reported. Among them, β-carbon elimination[3] and retro-allylation[1g,4] from metal alkoxides have been well exploited. Another talented approach to cleave sp^3C-sp^3C bonds utilizes highly stabilized carbanions including β-dicarbonyl enolates[5] and cyclopentadienyl anions[6] as leaving groups. Transition-metal-catalyzed synproportionation[5a,b] of allylmalonate derivatives is useful because of the importance of malonate chemistry in organic synthesis. Recently, Kotora described nickel-catalyzed deallylation of allylmalonates under mild conditions with organometallic reagents.[5c−f] Nevertheless, the allylic moieties of the malonate derivatives are simply cleaved off[5c−f] or transferred to another malonate anion[5a,b] without increasing molecular complexity and diversity. Herein, we report nickel-catalyzed arylative ring-opening of cyclic allylmalonate derivatives with arylzinc reagents. The new transformation increases molecular complexity and diversity starting from readily available precur-

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(1) (a) Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610–618. (b) Murakami, M.; Makino, M.; Ashida, S.; Matsuda, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1315–1321. (c) Satoh, T.; Miura, M. *J. Synth. Org. Chem. Jpn.* **2006**, *64*, 1199–1207. (d) Kondo, T.; Mitsudo, T. *Chem. Lett.* **2005**, *34*, 1462–1467. (e) Nakao, Y.; Hiyama, T. *J. Synth. Org. Chem. Jpn.* **2007**, *65*, 999–1008. (f) Nečas, D.; Kotora, M. *Curr. Org. Chem.* **2007**, *11*, 1566–1591. (g) Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 778–792.

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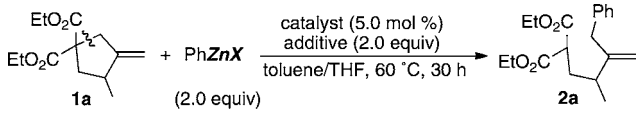
sors and allows us to regard a β-dicarbonyl moiety as a leaving or protective group, utilizing the allylic moieties as allylic electrophiles.

Treatment of diethyl 4-methyl-3-methylenecyclopentane-1,1-dicarboxylate (**1a**) with 2 equiv of phenylzinc bromide, which was prepared from zinc bromide and phenyl Grignard reagent in THF, in the presence of 5 mol % of $Ni(cod)_2$/$2PPh_3$ in toluene at room temperature afforded the corresponding product **2a** in 75% yield, and a part of **1a** still remained (Table 1, entry 1). The reaction was completed at

Table 1. Optimization of Reaction Conditions



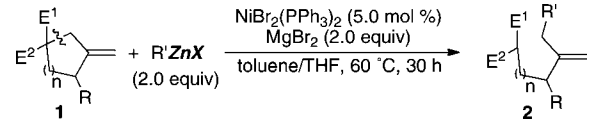
entry	catalyst	Ph***ZnX***	additive	yield[a]/%
1	$Ni(cod)_2/2PPh_3$	PhZnBr[b]	none	75[c,d]
2	$Ni(cod)_2/2PPh_3$	PhZnBr[b]	none	96
3	$Ni(cod)_2/2PPh_3$	PhZnI·LiCl	none	11[d]
4	$Ni(cod)_2/2PPh_3$	PhZnI·LiCl	$MgBr_2$	90
5	$NiBr_2(PPh_3)_2$	PhZnI·LiCl	$MgBr_2$	89
6	$Ni(acac)_2/2PPh_3$	PhZnI·LiCl	$MgBr_2$	89
7	$PdCl_2(PPh_3)_2$	PhZnI·LiCl	$MgBr_2$	12[d]
8	$Pd(PPh_3)_4$	PhZnI·LiCl	$MgBr_2$	26[d]
9	$CoCl_2(PPh_3)_2$	PhZnI·LiCl	$MgBr_2$	0[d]

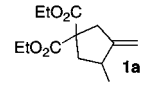
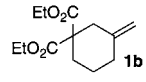
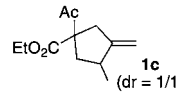
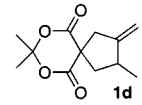
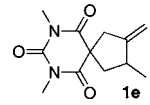
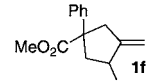
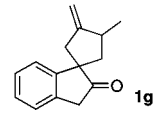
[a] Isolated yields. [b] Prepared from PhMgBr and $ZnBr_2$. The ring-opening reaction was performed for 8 h. [c] At room temperature. [d] NMR yields.

60 °C and gave **2a** in excellent yield (entry 2). Knochel's arylzinc iodide·lithium chloride complex[7] is easy to prepare from zinc powder and the corresponding aryl iodide in the presence of lithium chloride in THF, displaying an exceptionally broad range of functionalized zinc reagents. Hence, we applied the phenylzinc iodide·lithium chloride complex to the reaction. Disappointingly, product **2a** was obtained in only 11% yield (entry 3). However, an addition of magnesium bromide, which should be furnished in situ in the case of phenylzinc bromide in entries 1 and 2, dramatically increased the yield of the product up to 90% (entry 4). We assume that magnesium bromide promotes the sp^3C-sp^3C bond cleavage by working as a Lewis acid to activate dicarboxylate moiety (vide infra).[8] Alternatively, it might promote transmetalation between nickel and organozinc complexes.[9] Divalent nickel complexes, such as $NiBr_2(PPh_3)_2$ and $Ni(acac)_2/2PPh_3$, were effective as well as the expensive zerovalent nickel complex (entries 5 and 6). Other transition-metal catalysts were also examined. The product was obtained in low yield when di- or zerovalent palladium complex was used as a catalyst (entries 7 and 8). A cobalt complex failed to catalyze the ring-opening reaction (entry 9).

Various methylenecycloalkanes and arylzinc reagents were subjected to the optimized conditions (Table 1, entries 2 and 5), and the results are summarized in Table 2. The reactions

Table 2. Scope of Methylenecycloalkanes and Organozinc Reagents



entry	catalyst	R'***ZnX***[a]	2	yield/%[b]
1		4-MeC_6H_4ZnI•LiCl	**2b**	82
2	**1a**	4-$MeOC_6H_4ZnI$•LiCl	**2c**	85
3	**1a**	2-MeC_6H_4ZnBr	**2d**	93 (45)[c]
4	**1a**	4-FC_6H_4ZnI•LiCl	**2e**	90
5	**1a**	4-$EtO_2CC_6H_4ZnI$•LiCl	**2f**	59
6	**1a**	CH_2=CH(Ph)ZnI•LiCl	**2g**	66
7	**1a**	$C_6H_5CH_2ZnBr$[d]	**2h**	(28)[e]
8		PhZnBr	**2i**	95
9	 (dr = 1/1)	PhZnBr	**2j**	78[f] (dr = 1:1)
10		PhZnBr	**2k**	78[f]
11		PhZnBr	**2l**	92[f]
12		PhZnBr	**2m**	N.R.
13		PhZnBr	**2n**	N.R.

[a] PhZnBr and 2-MeC_6H_4ZnBr were prepared from the corresponding ArMgBr and $ZnBr_2$. No additional $MgBr_2$ needed. The ring-opening reaction was performed for 8 h. [b] Isolated yields. [c] The reaction was performed with 2-MeC_6H_4ZnI•LiCl for 30 h. [d] Prepared from $C_6H_5CH_2Br$ with Zn powder. [e] NMR yield. [f] At room temperature.

of methylenecyclopentane **1a** with 4-methylphenyl- and 4-methoxyphenylzinc reagents proceeded to afford the corresponding products in high yields (entries 1 and 2). Although the efficiency of the reaction with sterically hindered 2-methylphenylzinc iodide·lithium chloride was moderate, a high yield was obtained when 2-methylphenylzinc bromide was used (entry 3). The reactions of **1a** with

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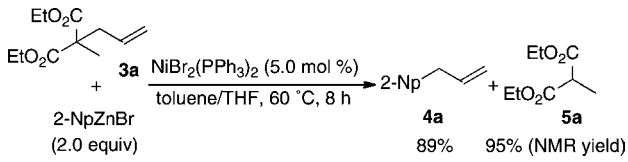
electron-deficient 4-fluorophenyl- and 4-ethoxycarbonylphenylzinc reagents provided the ring-opening arylated products in 90% and 59% yields, respectively (entries 4 and 5). An alkenylzinc reagent could be employed to give the desired product in 66% yield (entry 6). An attempt to perform the alkylative ring-opening with benzylzinc bromide resulted in the formation of the desired product in only 28% NMR yield (entry 7). Methylenecyclohexane **1b** underwent the arylative ring-opening smoothly to form **2i** in excellent yield (entry 8). Methylenecyclopentane **1c** having a β-ketoester part participated in the reaction with high efficiency at room temperature (entry 9). Cyclic 1,3-diester **1d**, which is readily available from Meldrum's acid,[10] was also more reactive than acyclic 1,3-diester substrates and easily transformed into **2k** at room temperature (entry 10). Moreover, not only diester and ketoester but also cyclic diamide **1e** was applicable and converted to arylative ring-opening product **2l** in 92% yield (entry 11). Unfortunately, no reaction took place when monoester **1f** or monoketone **1g** was used (entries 12 and 13). Thus, the dicarbonyl moieties proved to be essential for the success of the reaction.

We next investigated the reaction of acyclic substrates with an arylzinc reagent under nickel catalysis. The catalytic system is also effective for the reaction of diethyl allyl(methyl)malonate (**3a**) with 2-naphthylzinc bromide to yield 2-allylnaphthalene (**4a**) and diethyl methylmalonate (**5a**) as a byproduct (Scheme 1). This result encouraged us to

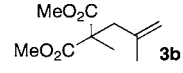
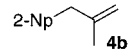
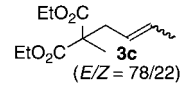
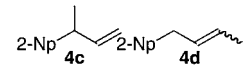
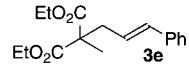
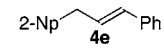
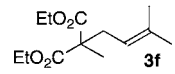
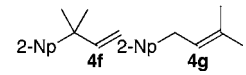
Scheme 1. Reaction of Allylmethylmalonate with 2-NpZnBr (2-Np = 2-Naphthyl)



examine the scope of various acyclic allylmalonate derivatives in the reaction, which is summarized in Table 3.

On treatment of **3b** bearing a methallyl group with 2-naphthylzinc bromide, a high yield of 2-methallylnaphthalene (**4b**) was obtained (Table 3, entry 1). Although the reaction of crotyl-substituted **3c** proceeded successfully, the products were obtained as a mixture of regio- and stereoisomers (entry 2). The lack of regio- and stereoselectivity indicates that the reaction pathway involves a π-allylnickel complex. Meanwhile, **4e** was obtained in quantitative yield as the sole product in the case of **3e** (entry 3). Attempted

Table 3. Scope of Allylmalonate Derivatives

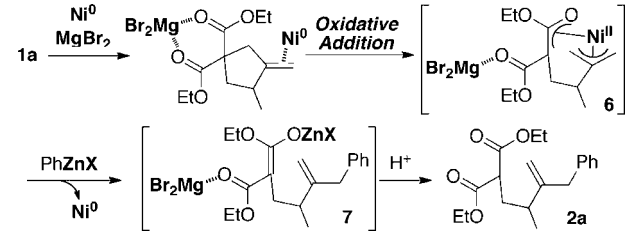
entry	catalyst	product **4**	yield/%[a]
1			85
2	 (*E*/*Z* = 78/22)		88[b]
3			quant.
4			N.R.

[a] Isolated yields. [b] **4c**/**4d** = 48/52. *E*/*Z* of **4d** = 71/29.

prenylation of 2-naphthylzinc bromide with **3f** failed due to its steric hindrance (entry 4).

On the basis of these facts, we propose the following reaction mechanism as shown in Scheme 2. Dicarbonyl

Scheme 2. Proposed Reaction Mechanism



compound **1a** coordinates to magnesium bromide. The coordination assists the oxidative addition to zerovalent nickel under cleavage of the sp^3C-sp^3C bond to form nickel complex **6**. Transmetalation between **6** and phenylzinc reagent followed by reductive elimination[11] gives zinc enolate **7**[12] and regenerates the starting nickel complex. Finally, protonolysis of the resulting zinc enolate **7** would provide **2a**.

Intermediate **7** could be trapped with various electrophiles. Treatment of the reaction mixture containing **7** with CD_3CO_2D gave **8a** (Table 4, entry 1). Furthermore, alkylation of zinc enolate **7**, the reactivity of which has been relatively unknown, with the reactive organic halides provided the corresponding products **8b**−**e** in good to excellent yields (entries 2−5).

A sequence of arylative ring-opening of **1b**, trapping with allyl bromide, and ring-closing metathesis[13] of **9** enabled formal

(8) Magnesium activates dicarbonyl compounds: (a) Yang, D.; Gao, Q.; Lee, C.-S.; Cheung, K.-K. *Org. Lett.* **2002**, *4*, 3271–3274. (b) Yang, D.; Li, J.-H.; Gao, Q.; Yan, Y.-L. *Org. Lett.* **2003**, *5*, 2869–2871. (c) Yip, K.-T.; Li, J.-H.; Lee, O.-Y.; Yang, D. *Org. Lett.* **2005**, *7*, 5717–5719. (d) Coscia, R. W.; Lambert, T. H. *J. Am. Chem. Soc.* **2009**, *131*, 2496–2498.

(9) Effect of magnesium salts on arylzinc reagents under nickel catalysis: Jin, L.; Liu, C.; Liu, J.; Hu, F.; Lan, Y.; Batsanov, A. S.; Howard, J. A. K.; Marder, T. B.; Lei, A. *J. Am. Chem. Soc.* **2009**, *131*, 16656–16657.

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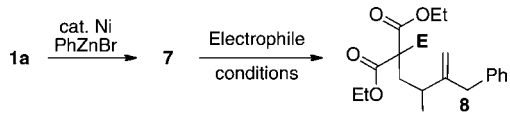
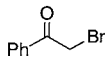
(12) Formation of zinc enolate via sp^3C-sp^3C bond cleavage: Sada, M.; Matsubara, S. *J. Am. Chem. Soc.* **2010**, *132*, 432–433.

(13) Sholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247–2250.

Table 4. Reaction of Electrophile with Zinc Enolate **7**



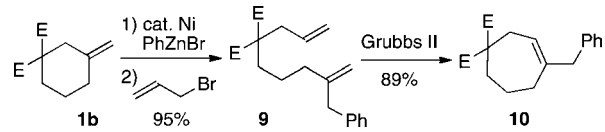
entry	reagent	E	product	conditions	yield %[a]
1	CD_3CO_2D	D	**8a**	60 °C/ 3 h	81[b]
2			**8b**	60 °C/10 h	96
3			**8c**	90 °C/10 h	78
4	MeI	Me	**8d**	90 °C/10 h	71
5			**8e**	90 °C/10 h	54

[a] Isolated yields. [b] 87% D.

arylative ring expansion of **1b** into cycloheptene **10**, which one can hardly accomplish by a different way (Scheme 3).

In summary, we have developed a nickel-catalyzed arylative ring-opening reaction of 3-methylenecycloalkane-1,1-dicarboxylate derivatives with arylzinc reagents. The reaction

Scheme 3. Arylative Ring Expansion (E = CO_2Et)



involves nickel-mediated ring-opening sp^3C-sp^3C bond cleavage, arylation of the allylic moiety, and the formation of the corresponding zinc enolate which is ready for further functionalization.

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Supporting Information Available: Characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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