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Highly Stereoselective Carbon–Carbon Bond-forming Reactions on Cyclopropane Rings Using 1-(Methoxycarbonyl)cyclopropylzinc Bromides

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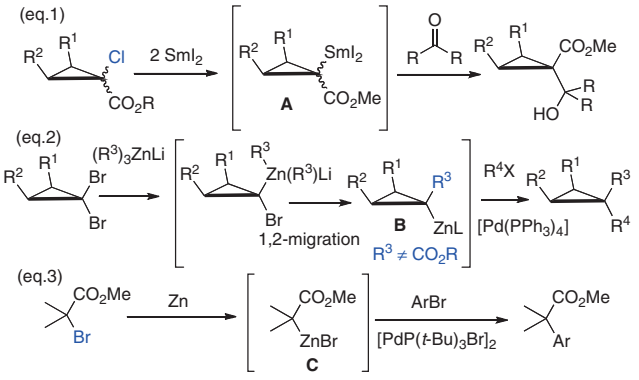
Highly stereoselective Reformatsky reaction and Pd-catalyzed arylation using 1-(alkoxycarbonyl)cyclopropylzinc bromide proceeded to give the *trans*-adduct as the major product in good to high yields with good to excellent stereoselectivities.

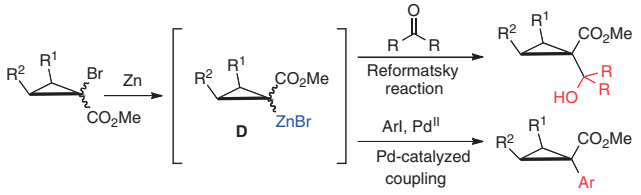
Zn-enolate is one of the useful reagents in organic chemistry.[1] The most representative synthetic protocol is the Reformatsky reaction.[2] During the course of our synthetic studies on the transformation of cyclopropanes,[3] we reported the SmI_2-promoted Reformatsky-type reaction of 1-chlorocyclopropanecarboxylate (Scheme 1, eq 1).[3a,3b] On the other hand, highly stereoselective C–C bond-forming reactions on cyclopropane rings are significantly important for the synthesis of pyrethroids and other biologically active cyclopropanes.[4,5] In 1993, Harada and Oku reported the stereoselective C–C bond-forming reactions of 1,1-dibromocyclopropanes via 1-halocyclopropyl zincates (Scheme 1, eq 2).[6] However, the fundamental Reformatsky reaction using Zn-enolate generated from 1-bromocyclopropanecarboxylic ester has not been investigated. In addition, although palladium-catalyzed arylation of Zn-enolate of α-bromo isobutyrate has been reported (Scheme 1, eq 3),[7] the Pd-catalyzed coupling[8] on a cyclopropane ring using Zn-enolate has not yet been investigated.

Here, we present highly stereoselective C–C bond-forming reactions using 1-(methoxycarbonyl)cyclopropylzinc bromide **D**, which includes the Reformatsky reaction and Pd-catalyzed coupling to afford a variety of tri- or tetrasubstituted cyclopropanes (Scheme 2).

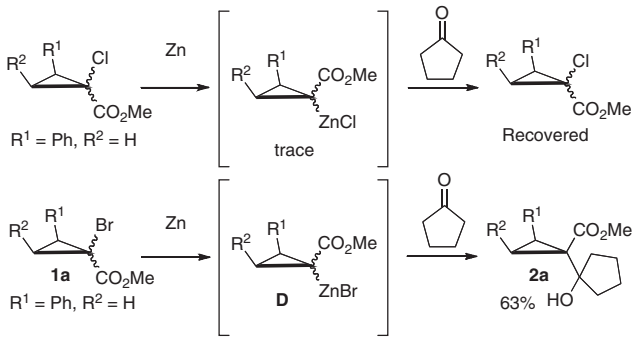
Initially, we tried to prepare the Zn-enolate from the α-chlorocyclopropanecarboxylic ester that was used in the SmI_2-promoted Reformatsky-type reaction.[3a] However, Zn-enolate was not generated from the α-chlorocyclopropanecarboxylic ester and starting material was recovered (Scheme 3). Thus, Zn-enolate has been prepared from bromoester **1a** that has a higher reactivity than the chloroester.[9] Treatment of Zn-enolate **D** with cyclopentanone resulted in a Reformatsky reaction to afford alcohol **2a** in high yield with excellent *trans*-selectivity (Scheme 3 and Table 1, Entry 1). This result encouraged us to investigate the Reformatsky reaction on a carbonylcyclopropane ring. Tables 1 and 2 list the results of the Reformatsky-type reaction of **1** with several aldehydes and ketones. The salient features were as follows: (i) α-bromocyclopropanecarboxylates **1a** and **1b** underwent the desired Reformatsky addition with



Scheme 1. Back-ground for this study.

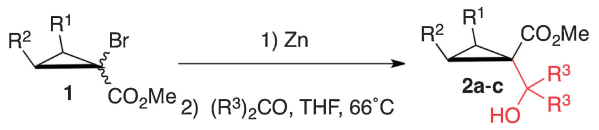


Scheme 2. C–C bond-forming reactions using Zn-enolate **D**.



Scheme 3. Initial investigations of the Reformatsky reaction using methyl α-halocyclopropanecarboxylates.

Table 1. Stereoselective Reformatsky reaction of α-bromoesters **1** with ketones

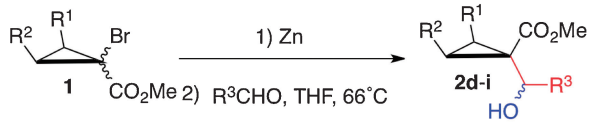


trans-add / *cis*-add > 99/1

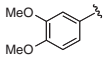
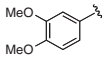
Entry	Substrate	R^1	R^2	R^3	Product	Yield[a]/%
1	**1a**	Ph	H	–$(CH_2)_4$–	**2a**	63
2	**1a**			Et	**2b**	61
3	**1a**			*i*-Pr	—	0
4	**1b**	–$(CH_2)_4$–		–$(CH_2)_4$–	**2c**	60
5	**1b**			Et	—	0
6	**1b**			*i*-Pr	—	0

[a]Isolated.

Table 2. Stereoselective Reformatsky reaction of α-bromoesters **1** with aldehydes



trans-add / *cis*-add > 99/1

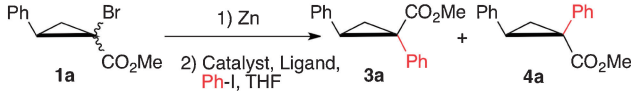
Entry	Substrate	R^1	R^2	R^3	Product	Yield[a]/%	dr[b]
1	**1a**	Ph	H	Ph	**2d**	92	56/44
2	**1a**				**2e**	96	62/38
3	**1a**			*n*-Hept	**2f**	74	60/40
4	**1b**	–$(CH_2)_4$–		Ph	**2g**	90	—
5	**1b**				**2h**	94	—
6	**1b**			*n*-Hept	**2i**	57	—

[a]Isolated. [b]Ratio was determined by ^{1}H NMR.

ketones to give *trans*-adducts **2a**, **2b**, and **2c**, respectively, in good yield with excellent *trans*-selectivity (*trans*-add/*cis*-add = >99/1) (Table 1, Entries 1, 2, and 4). (ii) A similar reaction of 2,3-*cis*-disubstituted cyclic substrate **1b** with cyclopentanone also gave the corresponding *trans*-adduct with excellent *trans*-selectivity (*trans*-add/*cis*-add = >99/1) (Table 1, Entry 4). (iii) Increase in the stereocongestion between the ketone and the substituted cyclopropane prevented the reaction from occurring (Entries 3, 5, and 6). (iv) Reactions of **1b** with aldehydes also proceeded to provide good to high yields with excellent *trans*-selectivities (*trans*-add/*cis*-add = >99/1) at the α-position and moderate diastereoselectivities[10] [**2** (*re*-face-adduct)/**3** (*si*-face-adduct) = 56/44–62/38] at the β-position (Table 2, Entries 1–3). Products **2d** and **2e** are important intermediates for the highly diastereoselective synthesis of dihydronaphthalene–lignan derivatives.[3e,3f]

These successful results led us to investigate the Pd-catalyzed coupling of the cyclopropyl-Zn-enolate, generated from α-bromo-β-phenylcyclopropanecarboxylates, with phenyl iodides. Optimizations of reaction conditions are summarized in Table 3. Treatment of the Zn-enolate, generated from **1a**, with iodobenzene at 66 °C in THF in the presence of $[Pd(PPh_3)_4]$ afforded diphenylcyclopropanecarboxylic esters **3a** and **4a** in 38% yield (Entry 1). In the cases of $Pd(OAc)_2$ with phosphine ligands, such as PPh_3, dppf, BINAP, JohnPhos adversely affected the coupling. Use of a tri(*o*-tolyl)phosphine ligand[7a] increased the yield of the coupling (Entry 4). The same reaction at room temperature resulted in decreased yield (Entry 5). In the case of $[Pd_2(dba)_2]$ rather than $Pd(OAc)_2$, a tri(*o*-tolyl)phosphine ligand also promoted the desired reaction to provide good to high yields (Entries 8 and 9). Use of four equivalents of the ligand increased the yield slightly. Buchwald ligands,[11] such as Johnphos, X-Phos, and S-Phos are also effective in promoting the coupling in moderate to good yields (48–68%) with good *trans*-selectivities (70/30–83/17). In the presence of PEPPSI-IPr, small amounts of esters **3a** and **4a** were obtained (Entry 13). Notably, the coupling reaction using $[PdP(t\text{-}Bu)_3Br]_2$[7a] promoted the reaction in high yield with high *trans*-selectivity (Entry 14). The same reaction at rt–50 °C gave **3a** and **4a** in 64% yield (Entry 15). Thus, the use of $[PdP(t\text{-}Bu)_3Br]_2$ at 66 °C in THF

Table 3. Stereoselective Pd-catalyzed coupling of α-bromoester **1a** with iodobenzene



Entry	Catalyst, Ligand	Pd/equiv	Temp./°C	Yield[a]/%	dr[b] (**3a**/**4a**)
1	$[Pd(PPh_3)_4]$	0.05	66	38	77/23
2	$Pd(OAc)_2$, 2 PPh_3	0.05	66	34	83/17
3	$Pd(OAc)_2$, dppf	0.05	66	35	83/17
4	$Pd(OAc)_2$, 2 P(*o*-Tol)$_3$	0.05	66	80	78/22
5	$Pd(OAc)_2$, 2 P(*o*-Tol)$_3$	0.05	rt	35	71/29
6	$Pd(OAc)_2$, 2 JohnPhos	0.05	66	57	78/22
7	$Pd(OAc)_2$, (*R*)-BINAP	0.05	66	39	87/13
8	$[Pd_2(dba)_3]$, 2 P(*o*-Tol)$_3$	0.05	66	76	36/64
9	$[Pd_2(dba)_3]$, 4 P(*o*-Tol)$_3$	0.05	66	82	42/58
10	$[Pd_2(dba)_3]$, 4 JohnPhos	0.05	66	48	74/26
11	$[Pd_2(dba)_3]$, 4 X-Phos	0.05	66	61	70/30
12	$[Pd_2(dba)_3]$, 4 S-Phos	0.05	66	68	83/17
13	Pd-PEPPSI-IPr	0.05	66	3	nd
14	$[PdP(t\text{-}Bu)_3Br]_2$	0.05	66	91	94/6
15	$[PdP(t\text{-}Bu)_3Br]_2$	0.05	rt-50	64	94/6

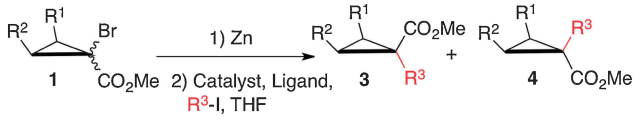
[a]Isolated. [b]Ratio was determined by ^{1}H NMR.

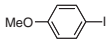
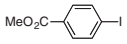
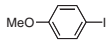
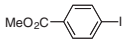
(method A) is the most efficient condition for this coupling (Entry 14). Other conditions involving $Pd(OAc)_2$ with two equivalents of P(*o*-Tol)$_3$ (method B) and $[Pd_2(dba)_3]$ with four equivalents of P(*o*-Tol)$_3$ (method C) are also considered to be practical conditions (Entries 4 and 9) even though the diastereomer ratios (dr) are moderate.

Next, we investigate the coupling reaction of cyclopropyl-Zn-enolate with several kinds of aryl or allyl iodide under the identified optimized conditions. The reaction of **1a** with *p*-anisyl iodide in the presence of $[PdP(t\text{-}Bu)_3Br]_2$ (method A) proceeded to give diarylcyclopropane **3b** as the major product in high yield with high *trans*-selectivity (Table 4, Entry 2). In the case of methyl *p*-iodobenzoate, the reaction proceeded to afford **3c** as the major product with minor diastereomer **4c** in moderate yield (Entry 4). Use of $Pd(OAc)_2$ with 2 equiv of P(*o*-Tol)$_3$ (method B) reversed the stereoselectivity (Entries 3 and 5). Under condition B, the coupling of **1a** with *o*-substituted phenyl iodide took place with high *trans*-selectivity (Entries 6 and 7). Under condition A, the same reaction of styryl iodide increased the yield of the coupling with high *trans*-selectivity (Entry 8). In the case of *cis*-disubstituted analog **1b** instead of **1a**, the coupling proceeded in 38–66% yields with excellent *trans*-selectivities (>99/1) (Entries 9–16). Regardless of the method (A, B, or C), yields and stereoselectivities (>99/1) were similar for reactions of **1b** (Entries 9–11). The electron-withdrawing group on the benzene ring decreased the yield of the coupling (Entry 13). This result is consistent with the reaction of **1a** (Entries 4 and 5). In the references and Supporting Information,[12] we considered the stereoselectivity based on the plausible transition state in the Pd-catalyzed coupling reaction of cyclopropyl-Zn-enolate with aryl iodide.

In conclusion, we achieved a few highly stereoselective syntheses of cyclopropane derivatives by using the Reformatsky reaction and Pd-catalyzed arylation of 1-(methoxycarbonyl)cyclopropylzinc bromide. The present methods are new avenues for the stereoselective synthesis of highly substituted cyclopropylcarbonyl compounds.

Table 4. Stereoselective Pd-catalyzed coupling of α-bromoesters **1** with aryl or alkenyl iodes



Entry	Substrate	R^1	R^2	R^3I	Product	Yield[d]/%	dr[e]
1	**1a**	Ph	H	PhI	**3a/4a**	91[a]	94/6
2					**3b/4b**	67[a]	88/12
3						71[b]	29/71
4					**3c/4c**	42[a]	87/13
5						40[b]	33/67
6					**3d/4d**	45[b]	97/3
7					**3e/4e**	57[b]	97/3
8					**3f/4f**	74[a]	95/5
9	**1b**	$-(CH_2)_4-$		PhI	**3g/4g**	66[c]	>99/1
10						64[b]	>99/1
11						60[a]	>99/1
12					**3h/4h**	63[c]	>99/1
13					**3i/4i**	38[c]	>99/1
14					**3j/4j**	61[c]	>99/1
15					**3k/4k**	63[c]	>99/1
16					**3l/4l**	52[a]	>99/1

[a]Method A: $[PdP(t\text{-}Bu)_3Br]_2$ (0.025 equiv). [b]Method B: $Pd(OAc)_2$ (0.050 equiv), 2 P(*o*-Tol)$_3$. [c]Method C: $[Pd_2(dba)_3]$ (0.025 equiv), 4 P(*o*-Tol)$_3$ (0.10 equiv). [d]Isolated. [e]Ratio was determined by ^{1}H NMR.

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Supporting Information is available electronically on J-STAGE.

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8 Negishi coupling ordinary does not include the coupling of Zn-enolate with aryl iodide under the presence of Pd catalyst. However, in extended view, because the Zn-enolate generated from α-haloester is presented in the C-enolate form (Zn-carbanion form), this reaction might be classified as expanded Negishi coupling.

9 A similar reaction of methyl 2-phenylcyclopropanecarboxylate using LDA with cyclopentanone gave **2a** in low yield (20%), because self-Claisen condensation mainly occurred (see, ref 3e).

10 The relative structure of *re*-/*si*-**2** (*re*-face-add/*si*-face-add) was assigned on the basis of the typical selectivity of SmI_2-promoted Reformatsky reaction (see ref 3a) and Shuto's report of highly stereoselective reduction of *trans*-substituted cyclopropanes; see: Y. Kazuta, H. Abe, T. Yamamoto, A. Matsuda, S. Shuto, *J. Org. Chem.* **2003**, *68*, 3511.

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12 A certain steric congestion around Pd in plausible transition states effectively increased the yield and *trans*-selectivity. In the coupling of **1a** (R^1 = Ph, R^2 = H) with iodobenzene, most bulky $(t\text{-}Bu)_3P$ ligand raises the *trans*-selectivity (94/6). In the case of less bulky P(*o*-Tol)$_3$ ligand, use of more bulky *o*-substituted phenyl iodide also enlarges the *trans*-selectivity (97/3). The coupling of *cis*-disubstituted cyclopropane **1b** with aryl iodides proceeds with excellent *trans*-selectivity (>99/1) owing to the steric repulsion between R^1, R^2, and aryl group. Thus, if one of the ligand, the aryl group or substituent on cyclopropane is sufficiently bulky, *trans*-selectivity would be increased. For detailed scheme, see SI p. 22.