

Catalytic Tandem C–C Bond Formation/Cleavage of Cyclopropene for Allylzincation of Aldehydes or Aldimine Using Organozinc Reagents

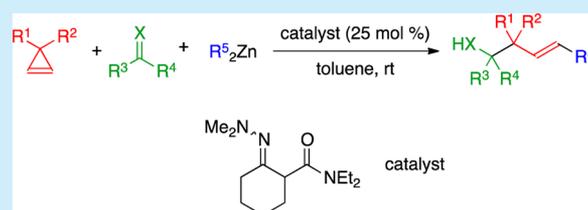
Takeo Nakano,[†] Kohei Endo,^{†,*‡} and Yutaka Ukaji[†]

[†]Division of Material Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma, Kanazawa 920-1192, Japan

[‡]PRESTO, Japan Science and Technology Agency (JST), 4-1-8 Honcho, Kawaguchi, Saitama 332-0012, Japan

S Supporting Information

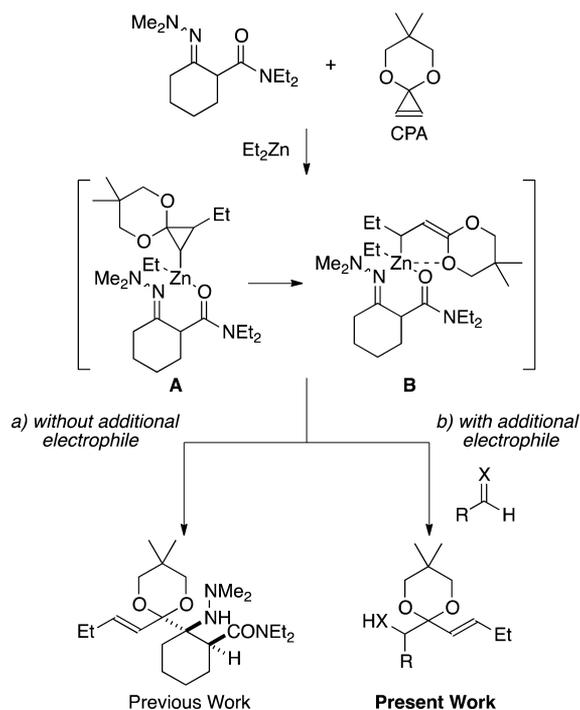
ABSTRACT: The tandem allylation of aldehydes or an aldimine with allylzinc intermediates derived from organozinc reagents and cyclopropenes is described. The present three-component reaction involves carbocation of cyclopropene and sequential cleavage of a cyclopropylzinc intermediate in situ without a transition-metal catalyst. The allylzinc intermediates generated in situ, which is an α,β -unsaturated acyl anion equivalent, gave the corresponding homoallylic alcohols or amine in good yields.



Activation of a C–C single bond in highly strained molecules is a powerful approach to the construction of structurally complex molecules in a single operation. However, previous reports have typically achieved C–C bond cleavage with the use of an expensive transition-metal catalyst, such as Pt, Rh, Ru, or Ir.¹ We previously reported the cleavage of cyclopropylzinc intermediates without a transition-metal catalyst to give allylzinc intermediates, which can take part in the allylzincation of β -hydrazoneamide derivatives in a single operation.² The transition-metal-free carbocation of cyclopropene in the presence of β -hydrazoneamide derivatives is a key factor in our approach to the tandem C–C bond cleavage in cyclopropylzinc intermediates.

Nucleophilic addition to electronically unactivated cyclopropene typically requires a transition metal as a catalyst.^{3,4} Marek and co-workers reported the Cu-catalyzed carbometalation of cyclopropene, oxidation, and retro aldol-type C–C bond cleavage.⁵ In contrast, our strategy using cyclopropenone acetal (CPA)⁶ as a cyclopropene for the carbocation proceeded without any metal catalyst to give a cyclopropylzinc intermediate in the presence of a β -hydrazoneamide, and subsequent C–C bond cleavage of a cyclopropylzinc intermediate took place in situ.⁷ Our previous report showed that the carbocation^{2,8} of CPA proceeded to give cyclopropylzinc intermediate A, the subsequent ring-opening of which generated allylzinc intermediate B for the chemoselective allylzincation of hydrazone (Scheme 1, a). Chemoselective C–C bond cleavage without a transition-metal catalyst gave the sterically congested hydrazone in a single operation. Although we have described the allylation of benzaldehyde in the presence of a stoichiometric amount of β -hydrazoneamide, the yield of the desired product was low. Since β -hydrazoneamides take part in the reaction as ligands as well as electrophiles, the allylation to other electrophiles may be difficult to control. We

Scheme 1. Allylzincation via Sequential Carbocation and C–C Bond Cleavage of Cyclopropylzinc Intermediate



report here the β -hydrazoneamide-catalyzed tandem carbocation of cyclopropene and the subsequent allylzincation of

Received: January 21, 2014

Published: February 24, 2014

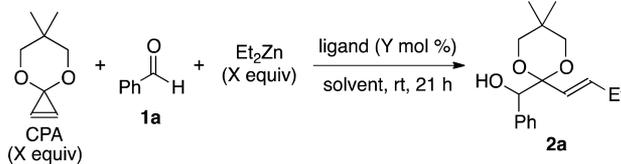
additional aldehydes and an aldimine as 3-component reactions in a single operation (Scheme 1, b).

The reaction conditions were examined for the β -hydrazoneamide-mediated or -catalyzed tandem allylzincation of benzaldehyde (**1a**) using diethylzinc and CPA (Table 1, Figure 1). The reaction without a ligand gave product **2a** in poor yield (entry 1).⁹ The use of cyclic hydrazoneamide **L1** as a ligand gave the desired product **2a** in moderate yield; other

ligands **L2** or **L3** promoted unidentified side reactions (entries 2–4). The ligands gradually gave a trace amount of byproducts via allylation to hydrazone and/or cyclopropylation, as reported previously.² The use of acyclic β -hydrazoneamide **L4** or **L5** gave the desired product **2a** in lower yields (entries 5 and 6). On the other hand, β -ketoamide **L6**, β -hydroxyhydrazone **L7**, amino alcohol **L8**, and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) did not give the product **2a** (entries 7–10). Therefore, the amounts of **L1**, diethylzinc, and CPA were examined. The reaction in the presence of a catalytic amount of **L1** (15 mol %) gave **2a** in 56% yield (entry 11). When the reaction was carried out at 0 °C, the yield of **2a** decreased (entry 12). Further screening of the reaction conditions in the presence of **L1** (25 mol %) showed that the reaction using diethylzinc (1.3 equiv) and CPA (1.3 equiv) gave the desired product **2a** in 76% yield (entries 13–17). The use of a coordinative solvent slowed the reaction (entries 18–23).

Under the optimized conditions, a catalytic tandem allylation reaction was performed using various aromatic and aliphatic aldehydes (Table 2). The reaction typically gave the (*E*)-isomer

Table 1. Optimization of Reaction Conditions



entry	ligand	solvent	X	Y	yield (%)
1		toluene	1.1	0	<10
2	L1	toluene	1.1	110	44
3	L2	toluene	1.1	110	nd
4	L3	toluene	1.1	110	20
5	L4	toluene	1.1	110	41
6	L5	toluene	1.1	110	trace
7	L6	toluene	1.1	110	nd
8	L7	toluene	1.1	110	nd
9	L8	toluene	1.1	110	nd
10	TMEDA ^b	toluene	1.1	110	nd
11	L1	toluene	1.1	15	56
12 ^a	L1	toluene	1.1	15	<33
13	L1	toluene	1.1	25	47
14	L1	toluene	1.2	25	70
15	L1	toluene	1.3	25	76
16	L1	toluene	1.4	25	65
17	L1	toluene	1.5	25	61
18	L1	benzene	1.3	25	63
19	L1	hexane	1.3	25	65
20	L1	THF	1.3	25	<7
21	L1	Et ₂ O	1.3	25	14
22	L1	MTBE	1.3	25	38
23	L1	CH ₂ Cl ₂	1.3	25	19

^aThe reaction was performed at 0 °C. ^bTMEDA is *N,N,N',N'*-tetramethylethylenediamine.

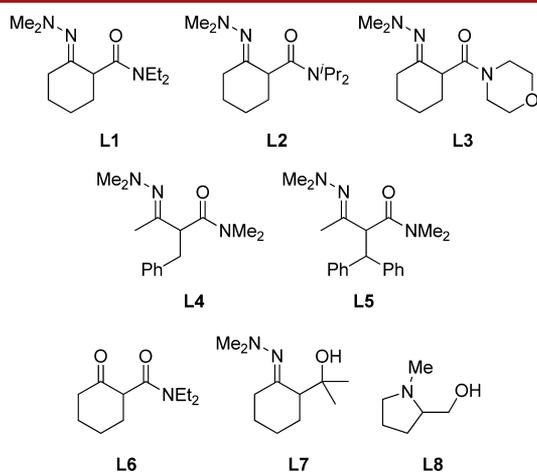
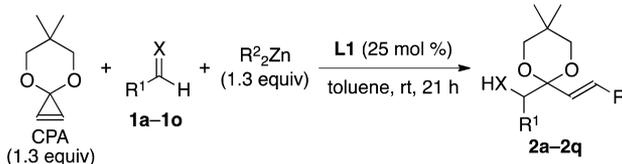


Figure 1. List of ligands.

Table 2. Scope of Substrates

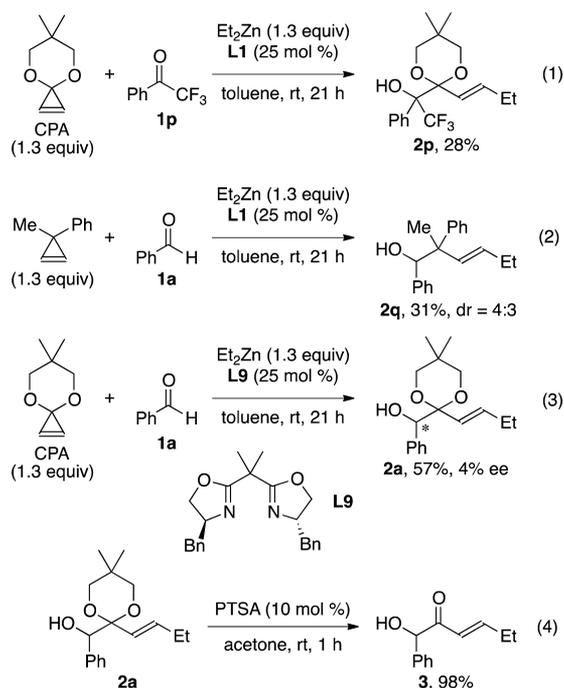


entry	R ¹ , X	R ²	yield (%)
1	Ph, O (1a)	Et	76 (2a)
2	Ph, O (1a)	Me	48 (2a-Me)
3	Ph, O (1a)	<i>i</i> -Pr	63 (2a-iPr)
4	2-MeC ₆ H ₄ , O (1b)	Et	62 (2b)
5	3-MeC ₆ H ₄ , O (1c)	Et	68 (2c)
6	4-MeC ₆ H ₄ , O (1d)	Et	71 (2d)
7	4-CF ₃ C ₆ H ₄ , O (1e)	Et	70 (2e)
8	4-MeOC ₆ H ₄ , O (1f)	Et	52 (2f)
9 ^a	4-FC ₆ H ₄ , O (1g)	Et	56 (2g)
10	1-naphthyl, O (1h)	Et	48 (2h)
11	2-naphthyl, O (1i)	Et	trace (2i)
12	2-furyl, O (1j)	Et	74 (2j)
13	2-phenylethyl, O (1k)	Et	73 (2k)
14	2-phenylethenyl, O (1l)	Et	68 (2l)
15	<i>c</i> -Hex, O (1m)	Et	77 (2m)
16	<i>t</i> -Bu, O (1n)	Et	35 (2n) ^b
17	Ph, NTs (1o)	Et	41 (2o)

^a**L1** (2 equiv), Et₂Zn (2 equiv), and CPA (2 equiv) were used. ^bThe product was isolated as a ketone after deprotection of acetal moiety.

as a sole or major product along with less than 5% of the (*Z*)-isomer. When Me₂Zn or *i*-Pr₂Zn was used instead of Et₂Zn, the allylation reaction of benzaldehyde (**1a**) proceeded to give the desired products **2a-Me** or **2a-iPr** (entries 2 and 3). When Ph₂Zn was used, the desired product was obtained in low yield, but the reaction was not reproducible. The reactions of 2-, 3-, or 4-methylbenzaldehyde (**1b–d**) gave the desired products **2b–d** in good yields (entries 4–6). When aromatic aldehydes **1e–g** bearing an electron-donating or -withdrawing group on the benzene ring were used, the corresponding products **2e–g** were obtained in moderate to good yields, respectively (entries 7–9). The use of 1- or 2-naphthaldehyde (**1h** or **1i**) decreased the yields of products **2h** or **2i** (entries 10 and 11). A

heteroaromatic aldehyde, 2-furfural (**1j**), was available (entry 12). The use of aliphatic aldehydes, such as dihydrocinnamaldehyde (**1k**), cinnamaldehyde (**1l**), and cyclohexanecarboxaldehyde (**1m**), gave the products **2k–m** in good yields (entries 13–15). The reaction of bulky pivalaldehyde (**1n**) diminished the yield of product; the acetal moiety partially decomposed on silica gel to give **2n**. The acidic deprotection after the reaction gave the product **2n** as a ketone (entry 16). The use of *N*-tosylimine (**1o**) gave the corresponding amine **2o** in moderate yield (entry 17). The reaction of ketone derivatives was examined, and the use of acetophenone gave the products in poor yield as a nonisolable mixture. In contrast, the use of 2,2,2-trifluoroacetophenone (**1p**) gave the desired product **2p** in 28% yield (eq 1). The reaction using simple cyclopropene gave the



product **2q** in low yield as a nonisolable diastereomeric mixture (eq 2). We tentatively examined the use of bisoxazoline **L9** as a chiral ligand for the asymmetric allylation reaction.¹⁰ The desired product **2a** was obtained, but the enantioselectivity was poor (eq 3). Deprotection of the acetal moiety of product **2a** proceeded in the presence of *p*-toluenesulfonic acid (PTSA) to give the corresponding α -hydroxy ketone **3** in almost quantitative yield (eq 4).

A plausible mechanism for the present reaction is shown in Figure 2. Initial carbozincation of cyclopropene in the presence of **L1** results in the formation of cyclopropylzinc intermediate **A**. Subsequent ring-opening generates the allylzinc intermediate **B**. The allylzincation of aldehyde proceeds to give the desired product, while the elimination of **L1** might occur. The oxygen atoms in CPA seem to play an important role in obtaining the desired products in good yields, since 3-methyl-3-phenylcyclopropene gave the desired product in low yield along with the generation of unidentified byproducts.

In conclusion, we have developed a catalytic tandem allylation of aldehydes, an aldimine, and a ketone with an allylzinc intermediate via carbozincation and a ring-opening sequence of cyclopropene. The present allylzinc intermediate acts as an α,β -unsaturated acyl anion equivalent and thus gives a wide variety of functionalized homoallylic alcohols or amine.

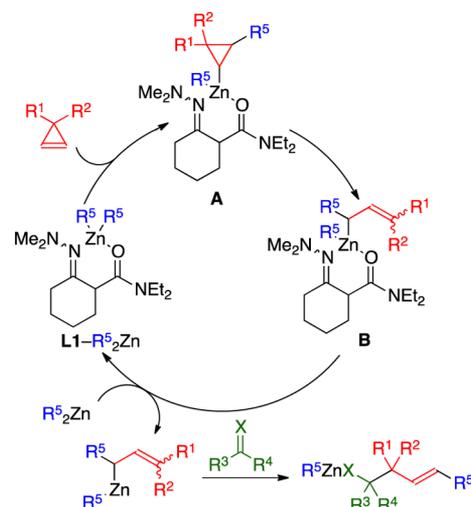


Figure 2. Plausible mechanism.

The allylzinc intermediates in the present report prepared in situ from stable cyclopropenes and commercially available dialkylzinc reagents would be useful for synthetic organic chemistry via an allylation reaction to give densely functionalized molecules in a one-pot procedure. Further studies on the chemoselective C–C bond cleavage are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and physical properties of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kendo@se.kanazawa-u.ac.jp

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the JST PRESTO program and a Grant-in-Aid for Scientific Research (B).

■ REFERENCES

- C–C bond activation: (a) Rybtchinski, B.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 870–883. (b) Seiser, T.; Cramer, N. *Org. Biomol. Chem.* **2009**, *7*, 2835–2840. (c) Murakami, M.; Matsuda, T. *Chem. Commun.* **2011**, 47, 1100–1105. (d) Seiser, T.; Saget, T.; Tran, D. N.; Cramer, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 7740–7752. (e) Ruhland, K. *Eur. J. Org. Chem.* **2012**, 2683–2706.
- Endo, K.; Nakano, T.; Fujinami, S.; Ukaji, Y. *Eur. J. Org. Chem.* **2013**, 6514–6518.
- Application of cyclopropenes; (a) Komatsu, K.; Kitagawa, T. *Chem. Rev.* **2003**, *103*, 1371–1428. (b) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117–3179. (c) Pallerla, M. K.; Fox, J. M. *Org. Lett.* **2007**, *9*, 5625–5628. (d) Xie, X.; Li, Y.; Fox, J. M. *Org. Lett.* **2013**, *15*, 1500–1503.
- Ring-opening of cyclopropenes with nucleophiles: (a) Ma, S.; Zhang, J.; Cai, Y.; Lu, L. *J. Am. Chem. Soc.* **2003**, *125*, 13954–13955. (b) Wang, Y.; Fordyce, E. A. F.; Chen, F. Y.; Lam, H. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 7350–7353. (c) Wang, Y.; Lam, H. W. *J. Org. Chem.* **2009**, *74*, 1353–1355. (d) Liu, Y.; Ma, S. *Chem. Sci.* **2011**, *2*,

811–814. (e) Chen, J.; Ni, S.; Ma, S. *Synlett* **2011**, 931–934. (f) Liu, Y.; Ma, S. *Org. Lett.* **2012**, *14*, 720–723. (g) Ni, S.; Chen, J.; Ma, S. *Org. Lett.* **2013**, *15*, 3290–3293.

(5) Delaye, P. -O.; Didier, D.; Marek, I. *Angew. Chem., Int. Ed.* **2013**, *52*, 5333–5337.

(6) Representative examples of cyclopropenone acetal: (a) Boger, D. L.; Zhu, Y. *J. Org. Chem.* **1994**, *59*, 3453–3458. (b) Kogen, H.; Kiho, T.; Tago, K.; Miyamoto, S.; Fujioka, T.; Otsuka, N.; Suzuki-Konagai, K.; Ogita, T. *J. Am. Chem. Soc.* **2000**, *122*, 1842–1843. (c) Nakamura, M.; Isobe, H.; Nakamura, E. *Chem. Rev.* **2003**, *103*, 1295–1326. (d) Poloukhine, A.; Popik, V. V. *J. Org. Chem.* **2005**, *70*, 1297–1305. (e) Patel, P. R.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 8527–8529.

(7) Ring-opening of cyclopropene with transition-metal catalyst: (a) Nakamura, I.; Bajracharya, G. B.; Yamamoto, Y. *J. Org. Chem.* **2003**, *68*, 2297–2299. (b) Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2007**, *129*, 3824–3825. (c) Hadfield, M. S.; Lee, A.-L. *Chem. Commun.* **2011**, *47*, 1333–1335.

(8) Representative examples of carbozincation: (a) Nakamura, E.; Kubota, K. *J. Org. Chem.* **1997**, *62*, 792–793. (b) Tarwade, V.; Liu, X.; Yan, N.; Fox, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 5382–5383. (c) Krämer, K.; Leong, P.; Lautens, M. *Org. Lett.* **2011**, *13*, 819–821.

(9) Enantioselective synthesis of homoallylic alcohols or amines: (a) Nokami, J.; Nomiyama, K.; Matsuda, S.; Imai, N.; Kataoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 1273–1276. (b) Nokami, J.; Nomiyama, K.; Shafi, S. M.; Kataoka, K. *Org. Lett.* **2004**, *6*, 1261–1264. (c) Yuan, Y.; Lai, A. J.; Kraml, C. M.; Lee, C. *Tetrahedron* **2006**, *62*, 11391–11396. (d) Sugiura, M.; Mori, C.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 11038–11039. (e) Tanaka, K.; Fujimori, Y.; Saikawa, Y.; Nakata, M. *J. Org. Chem.* **2008**, *73*, 6292–6298. (f) Lysenko, I. L.; Lee, H. G.; Cha, J. K. *Org. Lett.* **2009**, *11*, 3132–3134. (g) Tarselli, M. A.; Micalizio, G. C. *Org. Lett.* **2009**, *11*, 4596–4599. (h) Chen, M. Z.; McLaughlin, M.; Takahashi, M.; Tarselli, M. A.; Yang, D.; Umemura, S.; Micalizio, G. C. *J. Org. Chem.* **2010**, *75*, 8048–8059.

(10) Enantioselective allylzincation using bisoxazoline as a chiral ligand: (a) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **1996**, *118*, 8489–8490. (b) Nakamura, M.; Hirai, A.; Sogi, M.; Nakamura, E. *J. Am. Chem. Soc.* **1998**, *120*, 5846–5847. (c) Nakamura, M.; Inoue, T.; Sato, A.; Nakamura, E. *Org. Lett.* **2000**, *2*, 2193–2196.