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Synthesis of medium-sized carbocyclic ketones via the intramolecular *B*-alkyl Liebeskind–Srogl coupling reaction

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ABSTRACT

Synthesis of medium-sized carbocyclic ketones via the intramolecular *B*-alkyl Liebeskind–Srogl coupling reaction is described. The sequence of hydroboration of ω-alkenyl thiol ester with 9-BBN and the Liebeskind–Srogl reaction results in the formation of medium-sized carbocyclic ketones with good yield.

A medium-sized (8- to 11-membered) carbocyclic ketone is part of a number of biologically active terpenoids. For example, taxol (Fig. 1) is a clinically important anti-cancer agent with an 8-membered carbocyclic ketone. Therefore, the development of a synthetic method to construct medium-sized carbocyclic ketones has become an important research topic in synthetic organic chemistry.

In general, the structure of the ring being formed greatly influences the cyclization rate, which depends on the structure of the open chain initial state and the transition state structure that resembles the cyclic product. Therefore, the construction of a medium-sized ring through an intramolecular reaction is difficult because of the relatively large torsional strains and transannular strains that exist in such a ring. The formation of an 8-membered ring is a crucial step in the convergent total synthesis of taxol; however, the reported ring-formation yield does not exceed 50%.[1]

Reactive functional groups must be introduced at both ends of a substrate to ensure the formation of the desired ring through an intramolecular reaction. The probability that the functionalized chain terminals come sufficiently close such that they can react to form a ring decreases as the chain becomes longer, because the entropy change is negative when the open chain substrate is converted into the ring-shaped transition state.

In addition to the unfavorable entropy change, the reaction mode affects the efficiency of the ring formation. For instance, a nucleophile reacts from the back side of a leaving group in the S_N2 reaction (Scheme 1); hence, the formation of medium-sized rings through the intramolecular S_N2 reaction is difficult owing to the limited reaction mechanism. For example, 8-membered lactone takes the longest time to form in an intramolecular reaction of a number of ω-bromoalkane-carboxylate ions.[2]

Conversely, palladium-mediated ring formation proceeds via the oxidative addition of palladium, transmetalation to form a palladacycle, and reductive elimination to afford a cyclized product (Scheme 2). Thus, the reaction mechanism of palladium-mediated bond formation differs from that of the S_N2 reaction. The reductive elimination proceeds via the formation of a new C–C bond between the two cis-coordinating carbon atoms on the palladium catalyst; hence, for mechanistic reasons, palladium-mediated bond formation is suitable for the ring-formation reaction.

We have previously reported that the intramolecular *B*-alkyl Suzuki–Miyaura coupling reaction and palladium-mediated intramolecular alkenylation of methyl ketones efficiently form the taxane

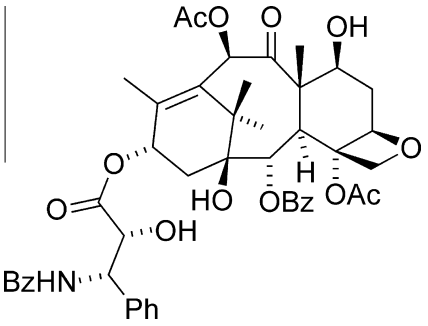

Figure 1. Structure of taxol.

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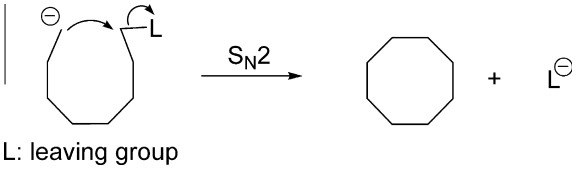
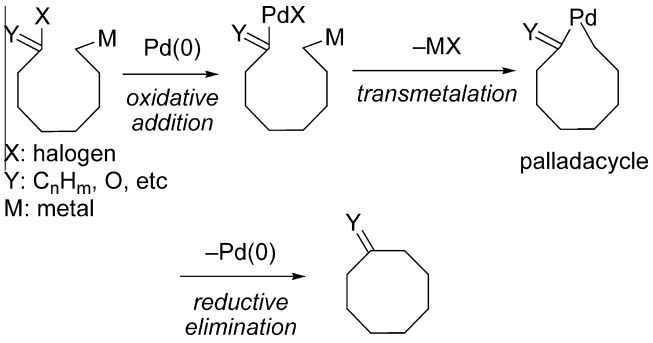


Scheme 1. Ring formation via the intramolecular S_N2 reaction.



Scheme 2. Ring formation via the palladium-mediated intramolecular reaction.

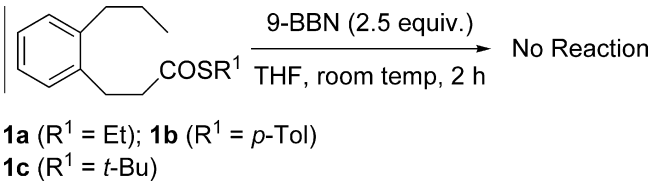
skeleton.[3] We now report the first example of the intramolecular *B*-alkyl Liebeskind–Srogl coupling reaction, which forms a medium-sized carbocyclic ketone with good yield.

In 2000, Liebeskind and Srogl reported a novel palladium-catalyzed C–C cross-coupling reaction to afford ketones from thioesters and boronic acids under neutral conditions (Scheme 3).[4] This reaction has been considerably extended to cross-coupling reactions between a variety of organosulfur and organometallic reagents because requisite organosulfur compounds—especially thiol esters—are easily prepared and relatively stable to handle.[5]

Morita and Kuwahara reported the intramolecular Liebeskind–Srogl coupling of the stannylated thioester to form a cyclopentenone ring.[6] However, to the best of our knowledge, an intramolecular Liebeskind–Srogl coupling reaction of the substrate with both the thiol ester and organoborane functionalities has never been reported, which is attributed to the difficulty of setting both the functionalities on a substrate. Liebeskind reported a Pd-mediated coupling reaction between a thiol ester and a borane derivative in the presence of a copper (I) salt.[7] Therefore, we expected the one-pot sequential reaction, which is the hydroboration of an ω-alkenyl carboxylic acid thiol ester and subsequent intramolecular Liebeskind–Srogl coupling reaction, can afford the corresponding carbocyclic ketone.

To establish this one-pot sequential reaction, the carboxylic acid thiol ester must remain intact while hydroboration of the terminal alkene is being carried out. Thiol esters are known to be more reactive than alkyl esters; hence, reactions with borane can occur. However, the reaction of **1a–c** with 9-BBN afforded almost no products under the conditions that are to be used for the hydroboration with 9-BBN in this study (Scheme 4).

To examine the sequence of hydroboration and Pd-catalyzed intramolecular reaction, we prepared thioethyl esters with a terminal alkene (Scheme 5). Thioethyl ester **4a** was easily prepared from



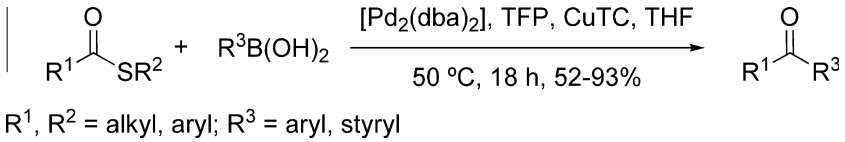
Scheme 4. Reaction of **1a–c** with 9-BBN.

the known compound **2**[8] via three steps: Stille coupling, hydrolysis of the methyl ester **3**, and thioethyl ester formation using DCC.

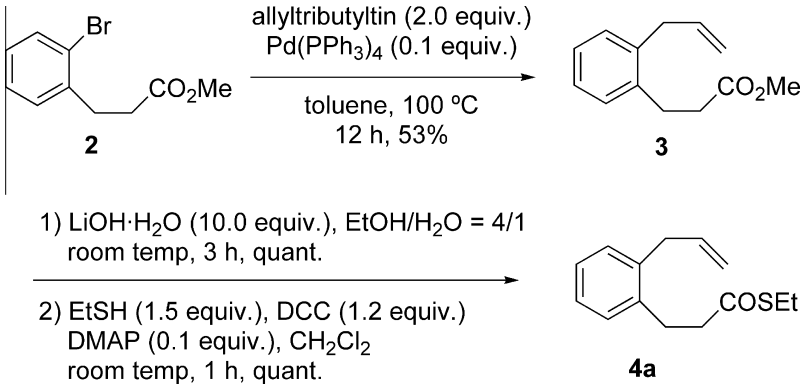
With **4a** in hand, we examined the reaction of **4a** and 9-BBN in THF; after the disappearance of **4a**, water was added to the reaction mixture to consume the remaining 9-BBN. Subsequently, the palladium-mediated intramolecular coupling reaction was examined under the Liebeskind conditions[7] used for the reaction of a *B*-alkyl 9-BBN; in other words, $Pd(PPh_3)_4$, CuTC, and Cs_2CO_3 were added to the reaction mixture, and the reaction was carried out at 50 °C under the highly diluted conditions (0.005 M) to avoid the intermolecular reaction.[9] As the termination of the coupling reaction could not be determined because the *B*-alkyl 9-BBN intermediate could not be detected by TLC, the coupling reaction was stopped after 40 h to isolate the product. The reaction of **4a** afforded **5** with 42% yield (Table 1, entry 1). The reaction using CsF as the base instead of $CsCO_3$ improved the yield (51%, entry 2). Hence, the reactions of **4b** and **4c** were examined using CsF. The yield of the reaction of *p*-toluenethiol ester **4b** was 48% (entry 3), and that of the reaction of *t*-butylthiol ester **4c** was 60% (entry 4). These results are interesting because the reaction of bulky *t*-butylthiol ester **4c** was surmised to be sluggish due to the steric hindrance, but **4c** gave better yield. The difference between the yields was also attributed to the instability of thiol esters **4a** and **4c** under basic conditions. The reaction of **4c** was examined under reflux conditions, but the yield was decreased (56%. entry 5).

We examined the reaction of **4c** using various solvents (entries 6–11); however, THF was found to be the best solvent. Regarding the base, the use of Na_2CO_3 (entry 12), K_2CO_3 (entry 13), 2,6-lutidine (entry 14), DBU (entry 15), and Et_3N (entry 16) decreased the yield; however, the reaction with DIPEA improved the yield to 80% (entry 17). The reaction time for all of the reactions of entries 1–17 was fixed as 40 h due to the aforementioned reasons; however, when the reaction time of entry 17 was shortened, the yield increased. After the reaction time was optimized, the yield improved to 91% when the reaction was carried out for 18 h (entry 18).[10] In general, the Liebeskind–Srogl coupling reaction proceeds without base.[5] In fact, the reaction of **4c** proceeded in the absence of base; however, the yield was low (entry 19). To improve the yield, the effects of various additives and Pd source were surveyed, too, but the yield was not improved.

As **4c** has ortho substituents on the benzene ring, both terminals of the chain are prone to come closer to undergo the ring-closing reaction. Moreover, the transannular interaction in **5** is reduced because **5** has an alkene in the ring. These factors may have led to a relative increase in the yield in the reaction of **4c**. Hence, to evaluate the efficiency, we examined the construction of saturated medium-sized carbocyclic ketones using our developed method. We prepared **8–10** by the alkylation reaction of **6** with **7** (Scheme 6)

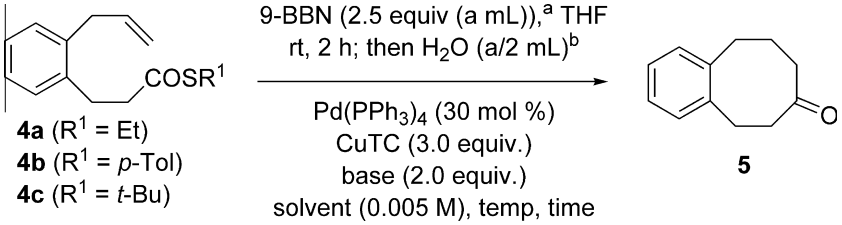


Scheme 3. Liebeskind–Srogl ketone synthesis.



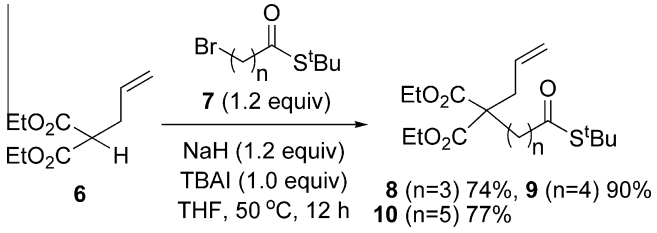
Scheme 5. Preparation of **4a**.

Table 1
The sequence of hydroboration of **4a–c** with 9-BBN and the Liebeskind–Srogl reaction to form 8-membered carbocyclic ketone **5**



Entry	Substrate	Solvent	Base	Temp (°C)	Time (h)	Yield[c] (%)
1	**4a**	THF	$CsCO_3$	50	40	42
2	**4a**	THF	CsF	50	40	51
3	**4b**	THF	CsF	50	40	48
4	**4c**	THF	CsF	50	40	60
5	**4c**	THF	CsF	reflux	40	56
6	**4c**	DMF	CsF	50	40	48
7	**4c**	1,4-dioxane	CsF	50	40	40
8	**4c**	CPME	CsF	50	40	30
9	**4c**	CH_3CN	CsF	50	40	54
10	**4c**	DMSO	CsF	50	40	51
11	**4c**	toluene	CsF	50	40	46
12	**4c**	THF	Na_2CO_3	50	40	29
13	**4c**	THF	K_2CO_3	50	40	45
14	**4c**	THF	2,6-lutidine	50	40	36
15	**4c**	THF	DBU	50	40	22
16	**4c**	THF	Et_3N	50	40	51
17	**4c**	THF	DIPEA	50	40	80
18	**4c**	THF	DIPEA	50	18	**91**
19	**4c**	THF	—	50	18	38

[a]A mL of 0.5 M THF solution was used. [b]A/2 mL of H_2O was used.
[c] Isotated yields.



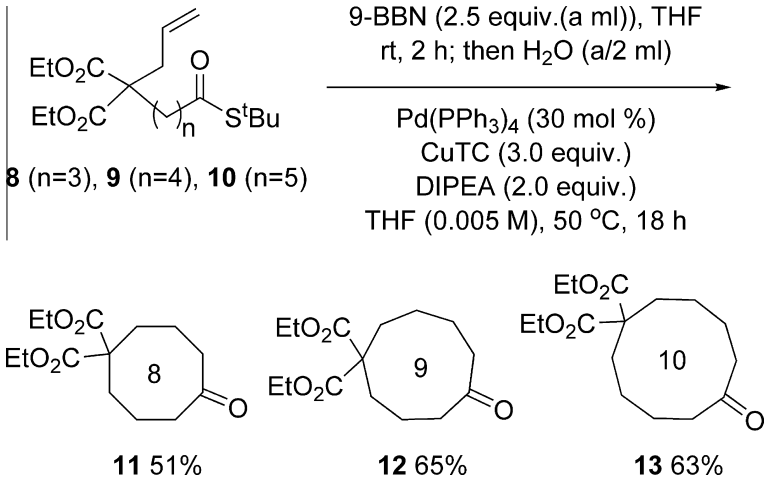
Scheme 6. Preparation of **8–10**.

and examined the ring-closing reaction under the conditions in entry 18 of Table 1.

Although, as expected, the yield of the reaction of **8** decreased compared with that of the reaction of **4c**, the saturated 8-membered ketone **11** was obtained with 51% yield (Scheme 7). The reaction of **9** afforded the saturated 9-membered ketone **12** with 65% yield, and the reaction of **10** afforded the saturated 10-membered ketone **13** with 63% yield.

In general, the saturated 9- and 10-membered carbocyclic rings are barely formed by ring-closing reactions. Hence, the results in Scheme 7 suggest that the method we developed may be widely applicable to the construction of medium-sized cyclic ketones.

In summary, we found that the sequence of hydroboration of ω-alkenyl thiol ester with 9-BBN and the Liebeskind–Srogl reaction results in the formation of medium-sized carbocyclic ketones with good yield. This is the first successful example of the intramolecular *B*-alkyl Liebeskind–Srogl reaction. The ring-closing reaction of the substrate with two terminals that easily come close to each other proceeded with excellent yield; hence, the method reported here should be applicable to the synthesis of other ring systems.



Scheme 7. The sequence of hydroboration of **8**–**10** with 9-BBN and the Liebeskind–Srogl reaction to form medium-sized carbocyclic ketones **11–13**.

Acknowledgments

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9. The highly diluted conditions (0.005 M) were crucial for the good yield. When the reaction was carried out using a 0.1 M solution of the substrate, the yield of **5** was decreased to 45% even under the conditions emplyed in entry 18 of Table 1.
10. *Preparation of 5 from 4c:* To a stirred solution of *S*-tert-butyl 3-(2-allylphenyl)propanethioate **4c** (30 mg, 0.114 mmol) in THF (0.23 mL) was added a solution of 9-BBN in THF (0.57 mL, 0.5 M, 0.285 mmol) dropwise at 30 °C and the resultant solution was stirred until the starting material disappeared. The reaction was quenched with H_2O (0.28 mL) and the resultant mixture was stirred at room temperature for 5 min. Then, to the reaction mixture were added THF (22.6 mL), Pd $(PPh_3)_4$ (39.6 mg, 3.42×10^{-2} mmol), Cu (I) thiophene-2-carboxylate (65.4 mg, 0.342 mmol), and DIPEA (0.04 mL, 0.228 mmol), and the mixture was stirred at 50 °C for 18 h. To the reaction mixture were added Et_2O (2 mL), a saturated aqueous NH_4Cl (2 mL) solution, and water (2 mL). The aqueous layer was separated and extracted with Et_2O (2 mL × 2). The combined organic layers were washed with brine (2 mL × 1), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1), and further purification by PTLC (hexane/ethyl acetate = 4/1) afforded 5,6,9,10-tetrahydrobenzo[8]annulen-7(8*H*)-one **5** (18.1 mg, 91%). **5**: R_f = 0.48 (hexane/ethyl acetate = 4/1); mp: 42.1–48.7 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.10 (4H, m), 3.03 (2H, dd, *J* = 6.8, 6.3), 2.75 (2H, dd, *J* = 6.3, 6.1), 2.65 (2H, dd, *J* = 6.8, 6.3), 2.31 (2H, dd, *J* = 6.6, 6.3), 1.86–1.80 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.7, 139.4, 139.1, 129.8, 129.4, 127.4, 126.9, 49.2, 39.8, 32.5, 29.2, 27.2; IR (solid) ν_{max} 3018, 2937, 1701, 1216, 754 cm^{-1}; HRMS (EI) $[M]^+$ calcd for $C_{12}H_{14}O$: 174.1045, found: 174.1047.