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Synthesis of Cyclopropane Fatty Acids by C(sp^3)–C(sp^3) Cross-coupling Reaction and Formal Synthesis of α-Mycolic Acid

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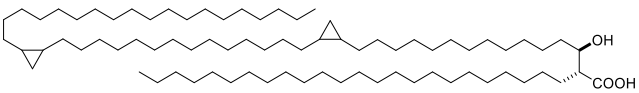
Abstract. An iterative Ni-catalyzed C(sp^3)–C(sp^3) cross-coupling reaction of a novel *cis*-cyclopropane containing bifunctional building blocks with alkyl halides and alkyl Grignard reagents enabled the introduction of a cyclopropane ring into the desired position(s) of saturated carbon frameworks, providing a straightforward synthetic route to cyclopropane fatty acids. The present method creates a direct route for the construction of saturated carbon frameworks, and can avoid the tedious multistep operations based on unsaturated functional group manipulations that are often employed in conventional synthetic routes. This method could be applicable to the synthesis of *trans*-cyclopropane fatty acids and enantioenriched cyclopropane fatty acids. Formal synthesis of α-mycolic acid was achieved by the C(sp^3)–C(sp^3) cross-coupling reaction of cyclopropane-containing bifunctional building blocks.

Keywords: alkylation; cyclopropane; C–C coupling; fatty acids; mycolic acids

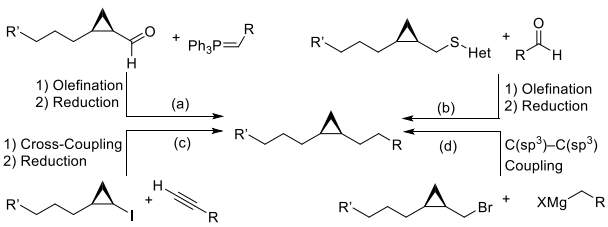
Introduction

cis-Cyclopropane rings are biologically synthesized by CFA synthase[1] and found in microorganisms,[2] protozoa,[3] and plants[4] as cyclopropane fatty acids (CFAs) and their phospholipids and glycolipids. In addition, owing to its unique structural motif, the cyclopropane moiety is often used in drug development as a bioisostere of olefins, amides, and other compounds.[5] A simple route to access CFAs is the cyclopropanation of the corresponding unsaturated fatty acid. However, there are some drawbacks: the stereoselective construction of cyclopropane rings is difficult, and only CFAs with available parent unsaturated fatty acids are accessible. To synthesize CFAs and their bioactive derivatives such as lipids, the construction of not only the cyclopropane rings,[6] but also of saturated hydrocarbon frameworks are important. For instance, a class of long CFAs, mycolic acids, has one or two cyclopropane ring(s) in a saturated 60- to 90-carbon chain, as represented by α-mycolic acid shown in Scheme 1.[7] Therefore,



Scheme 1. Structure of α-Mycolic Acid (**1**)

combining building blocks that contain a cyclopropane ring and saturated carbon chain(s) is a more rational route to access CFAs.[8] In this context,



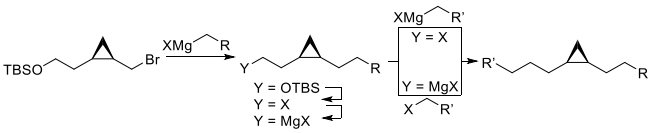
Scheme 2. Synthetic routes of alkyl chains including a cyclopropane ring.

some cyclopropane building blocks have been developed for the total synthesis of CFAs and employed in the synthesis of enantioenriched CFAs.[9] These building blocks, however, require multistep manipulations, including Wittig and Julia-type olefination or the introduction of alkyne units and the subsequent reduction of the unsaturated bonds to alkyl chains (Scheme 2a-c).

A good alternative method to attach a carbon chain to a cyclopropane building block is a transition-metal-catalyzed cross-coupling reaction.[10-12] Recently, the authors (Y.F. and K.F.) reported the total synthesis of cardiolipins using cross-coupling reactions, where a Pd-catalyzed Sonogashira-type cross-coupling reaction followed by reduction of the C–C triple bond (Scheme 2c) was used to connect an alkyl group and a cyclopropane, along with Cu-catalyzed alkyl-alkyl cross-coupling for the further extension of the saturated carbon chain.[13]

We have reported Ni, Cu, Co, and Fe-catalyzed cross-coupling reactions of alkyl halides with alkyl Grignard reagents in the presence of unsaturated hydrocarbon additives as promising routes for the construction of saturated hydrocarbon frameworks.[14] These alkyl-alkyl cross-coupling reactions are useful for the preparation of fatty acids and their derivatives, including glycerolipids and sphingolipids.[15,16] In addition, *trans*-fatty acids were synthesized using *trans*-6-bromo-1-(*tert*-butyldimethylsiloxy)-3-hexene as a *trans*-olefin building block.[15]

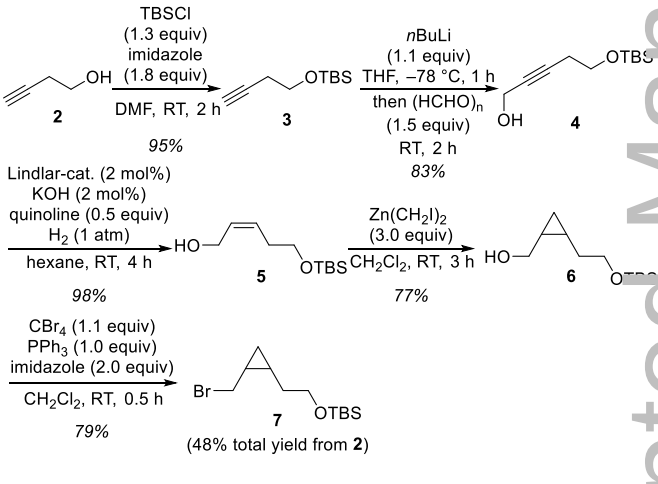
These successful results prompted us to investigate a practical synthetic route to access CFAs using building blocks containing a cyclopropane (Scheme 2d). Scheme 3 depicts our strategy, in which we devised an unsymmetric cyclopropane building block having bromomethyl and 2-siloxyethyl groups on the cyclopropane ring. The cross-coupling reaction at the C–Br bond of the building block with an alkyl Grignard reagent enables the single-step introduction of a saturated hydrocarbon chain. The siloxy group in the coupling product can be transformed into a halogen group (X) in one step and subsequently used in the cross-coupling reactions to access CFAs. When a building block carrying a *trans*-cyclopropane ring or an enantioenriched building block is used, *trans*-CFAs or enantioenriched CFAs, respectively, are expected to be synthetized in a similar way. Herein, we report the synthesis of novel building blocks carrying a *cis*- or *trans*-cyclopropane ring, and the results of assembling CFAs by $C(sp^3)$–$C(sp^3)$ cross-coupling reactions employing the building blocks. This could be used in the formal synthesis of a cyclopropane-containing long fatty acid, α-mycolic acid, following a reported procedure.[17]



Scheme 3. Synthesis of CFAs using a cyclopropane-containing building block.

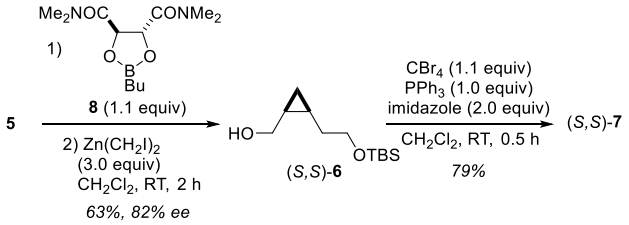
Results and Discussion

cis-Cyclopropane-containing building block **7** was synthesized from commercially available homopropargyl alcohol **2** (Scheme 4). Homologation of the protected homopropargyl alcohol **3** via lithiation and subsequent trapping by formaldehyde afforded **4**. Stereoselective hydrogenation of the internal alkyne **4** by Lindlar catalyst gave *cis*-allylic alcohol **5**.[18] The cyclopropanation of **5** by $Zn(CH_2I)_2$ proceeded smoothly to give *cis*-cyclopropane-containing monosilylated diol **6** as the sole stereoisomer in 77% yield. Subsequent bromination of the hydroxy group by CBr_4-PPh_3 afforded the *cis*-cyclopropane building block **7** in 79% yield.



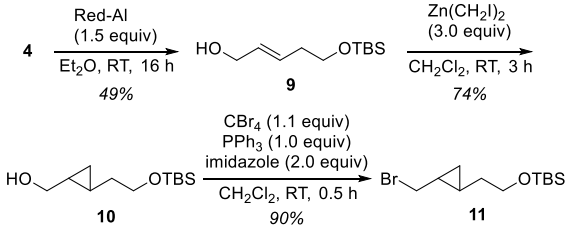
Scheme 4. Synthesis of *cis*-cyclopropane-containing building block **7**.

As shown in Scheme 5, asymmetric cyclopropanation of *cis*-allylic alcohol **5** by the combined use of the chiral borane reagent **8** and $Zn(CH_2I)_2$ as reported by Charette[19] afforded the optically active **6** in 82% enantiomeric excess (ee), suggesting that the present synthetic route could be applicable to the asymmetric synthesis of CFAs (*vide infra*).



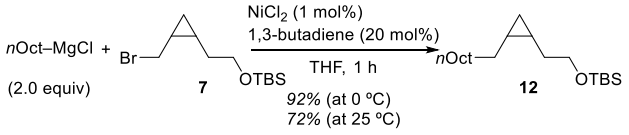
Scheme 5. Asymmetric synthesis of building block **7**.

A building block containing a *trans*-cyclopropane was also synthesized in a similar manner. Sodium bis(2-methoxyethoxy) aluminum hydride (Red-Al)-mediated *trans*-selective reduction of the common intermediate **4** afforded *trans*-allylic alcohol **9**. The cyclopropanation of **9** by $Zn(CH_2I)_2$ and the subsequent bromination of the hydroxy group in compound **10** gave the corresponding *trans*-cyclopropane-containing building block **11** (Scheme 6).



Scheme 6. Synthesis of *trans*-cyclopropane-containing building block **11**.

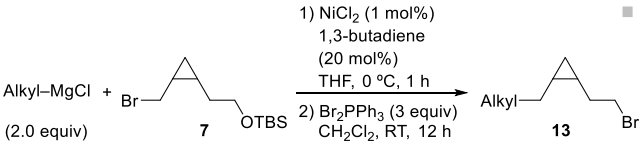
With building blocks bearing a cyclopropane ring in hand, we next examined the cross-coupling reaction of building block **7** with an alkyl Grignard reagent (Scheme 7). The cross-coupling reaction of building block **7** with *n*OctMgCl in the presence of 1 mol% of $NiCl_2$ and 20 mol% of 1,3-butadiene[14a] in THF at 25 ºC afforded the corresponding coupling product **12** in 72% yield. Lowering the reaction temperature to 0 ºC improved the yield of **12** to 92%. It should be noted that the bromide **7** could undergo a ring-opening reaction of the cyclopropane when the corresponding alkyl radical is generated via electron transfer; however, no evidence of the radical ring-opening was observed under the reaction conditions. This result is consistent with our mechanistic studies on the Ni/1,3-butadiene catalytic system.[14a,20] In contrast, the attempt to generate the corresponding Grignard reagent from bromide **7** under standard conditions failed due to the radical opening of the cyclopropane ring.



Scheme 7. $C(sp^3)$–$C(sp^3)$ coupling reaction of building block **7** with an alkyl Grignard reagent.

Using building block **7**, we attempted the synthesis of an analogue of (*Z*)-octadec-9-enoic acid, oleic acid (C18:1), having a *cis*-cyclopropane ring instead of the *cis*-olefin and its analogues. We conducted the Ni-catalyzed cross-coupling reaction of bromide **7** with various alkyl Grignard reagents under the optimized conditions, and subjected the crude coupling products to bromination by in situ generated Br_2PPh_3 to afford the corresponding bromide **13**. Table 1 summarizes the yields of the two-step manipulations, where the somewhat lower yields for Et and *n*Pr Grignard

Table 1. $C(sp^3)$–$C(sp^3)$ coupling reaction of building block **7** with alkyl Grignard reagents.



Entry	AlkylMgCl	**13**	Yield [%]
1	EtMgCl	**13a**, ω-4	59
2	*n*PrMgCl	**13b**, ω-5	57
3	*n*BuMgCl	**13c**, ω-6	70
4	*n*PenMgCl	**13d**, ω-7	69
5	*n*HexMgCl	**13e**, ω-8	93
6	*n*HepMgCl	**13f**, ω-9	75
7	*n*OctMgCl	**13g**, ω-10	61
8	*n*NonMgCl	**13h**, ω-11	72

reagents are probably due to the volatility of the resulting bromides **13a** and **13b**.

Next, we examined the cross-coupling reaction of bromide **13** with bromoalkanoic acid **14** to produce CFAs. We have previously reported the cross-coupling reaction of in situ protected bromoalkanoates **14**, formed by the treatment of bromoalkanoic acids with *t*BuMgCl, with alkyl Grignard reagents to synthesize various fatty acids.[15] Using the same in situ protection, an analogue of oleic acid (C18:1) having a cyclopropane ring (**15f**) was obtained in 55% yield by the Ni/1,3-butadiene-catalyzed cross-coupling reaction of in situ generated Grignard reagent with magnesium 5-bromohexanoate **14** (n = 5) (Table 2, entry 6). By changing the carbon length of the coupling partners, its regioisomers carrying the *cis*-cyclopropane ring at the ω-4 to ω-11 positions were obtained in moderate yields (entries 1-5 and 7-8). In addition, CFAs consisting of different carbon lengths, i.e., (*Z*)-hexadec-9-enoic acid and (*Z*)-icos-9-enoic

Table 2. Synthesis of *cis*-CFAs.

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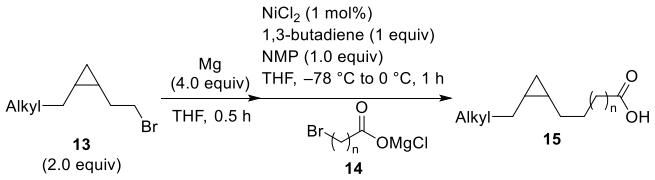
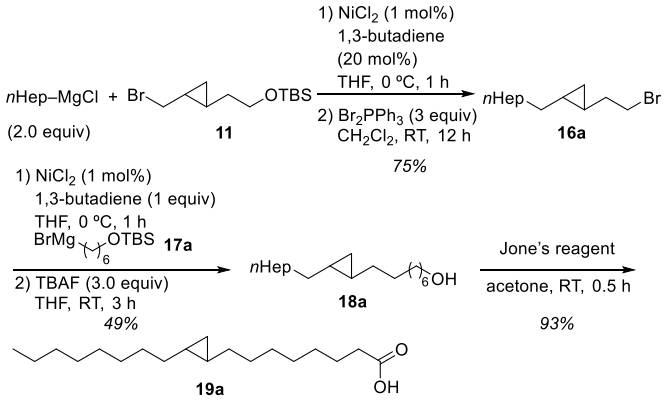


Entry	Alkyl	n of **14**	**15**	Yield [%]
1	Et	10	**15a** (C18:1, ω-4)	51
2	*n*Pr	9	**15b** (C18:1, ω-5)	52[a)]
3	*n*Bu	8	**15c** (C18:1, ω-6)	63
4	*n*Pen	7	**15d** (C18:1, ω-7)	55
5	*n*Hex	6	**15e** (C18:1, ω-8)	56
6	*n*Hep	5	**15f** (C18:1, ω-9)	55
7	*n*Oct	4	**15g** (C18:1, ω-10)	59
8	*n*Non	3	**15h** (C18:1, ω-11)	58
9	*n*Hep	3	**15i** (C16:1, ω-9)	64
10	*n*Hep	7	**15j** (C20:1, ω-9)	54

[a)] Isolated as the corresponding Me ester.

acid, were synthesized in the same manner in good yields (entries 9 and 10). These results demonstrate the versatility of the present synthetic method for the synthesis of various CFAs.

Next, the introduction of a *trans*-cyclopropane ring into the fatty acids was examined using the *trans*-cyclopropane building block **11**. Under the same conditions as shown in Table 1, the coupling reaction of building block **11** with *n*HepMgCl proceeded smoothly to give the corresponding coupling product **16a** in 75% yield after bromination of the siloxy group (Scheme 8).



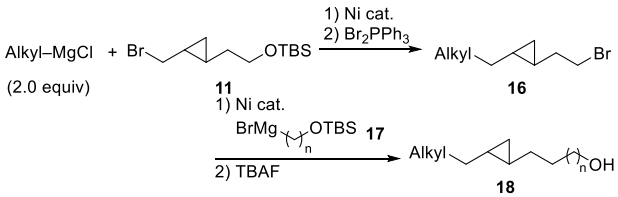
Scheme 8. Synthesis of an analogue of elaidic acid having a *trans*-cyclopropane.

As seen in Scheme 3, the obtained bromides can be used as both bromides (Scheme 3, top) and Grignard reagents (Scheme 3, bottom) in the successive coupling reaction. We thus conducted the subsequent coupling reaction of bromide **16a** with siloxyhexyl Grignard reagent **17a** in the presence of 1 mol% of $NiCl_2$ and 1 equiv of 1,3-butadiene in THF, and obtained the corresponding coupling product **18a** in 49% yield after deprotection of the silyl group by tetrabutylammonium fluoride (TBAF). An analogue of elaidic acid, a *trans*-fatty acid (C18:1), having a *trans*-cyclopropane ring instead of the *trans*-olefin, was successfully synthesized by Jones oxidation of the hydroxy group in 93% yield (Scheme 8).

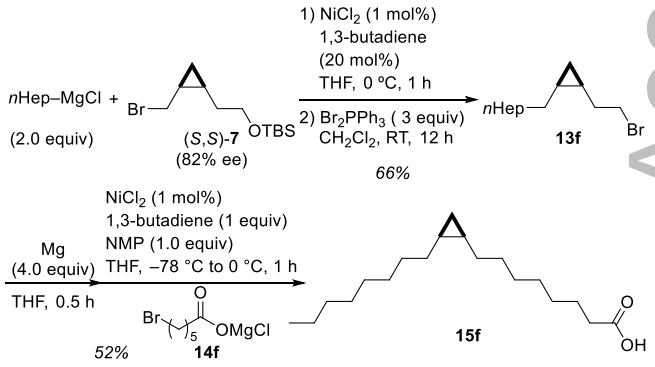
Table 3 summarizes the results of the coupling reactions of **11** with various alkyl Grignard reagents followed by the second coupling reaction of the thus formed bromides **16** with ω-siloxyalkyl Grignard reagents **17** to afford **18**, which has a *trans*-cyclopropane ring at a different position from that of **18a**. Both the first and second cross-coupling reactions, along with the functional group transformations, proceeded smoothly, giving rise to the correspond alcohols **18b-g**, bearing a cyclopropane ring at the ω-4 to ω-10 positions, in moderate yields.

Because a cyclopropane ring consists of sp^3-carbons, it could contain a chiral center. Therefore, the stereocontrolled synthesis of CFAs and related compounds is important for the study of their biological activities. We thus investigated the stability

Table 3. Synthesis of **18** bearing a *trans*-cyclopropane ring at different positions.



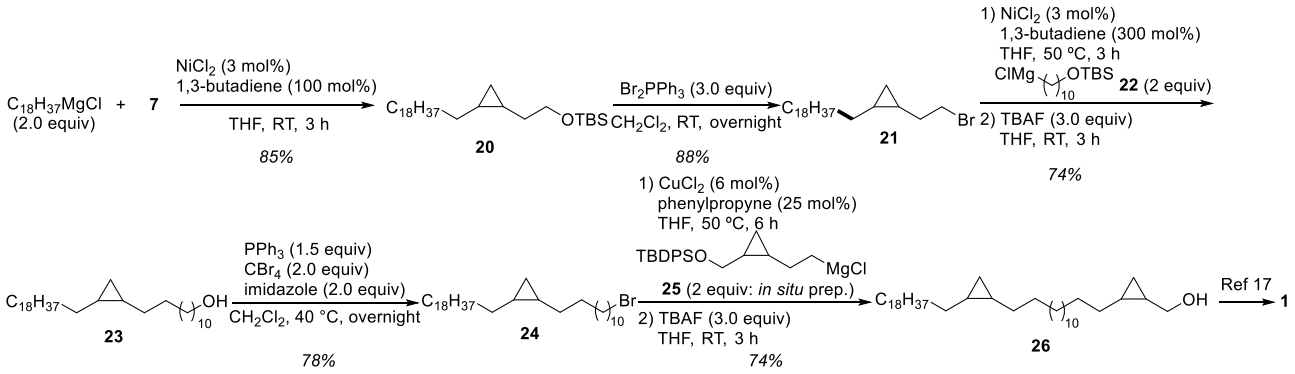
Entry	Alkyl	n of **17**	**18**	Yield [%]	
				16	**18**
1	EtMgCl	11	**18b**, ω-4	38	52
2	*n*PrMgCl	10	**18c**, ω-5	40	54
3	*n*BuMgCl	9	**18d**, ω-6	46	62
4	*n*PenMgCl	8	**18e**, ω-7	69	53
5	*n*HexMgCl	7	**18f**, ω-8	96	56
6	*n*OctMgCl	5	**18g**, ω-10	66	52



Scheme 9. Synthesis of an enantioenriched CFA.

of the chiral center of the enantioenriched building block **7** (Scheme 5) throughout the present synthetic route. The reaction of (*S*,*S*)-**7** with *n*HepMgCl afforded the corresponding coupling product **13f** in 66% yield, where no epimerization of the β-chiral center of **7**, namely isomerization into a *trans*-cyclopropane, was observed. This result indicates that the β-carbon of the reacting carbon center is stereochemically stable under the present $C(sp^3)$–$C(sp^3)$ coupling reaction. The subsequent coupling reaction of the corresponding Grignard reagent with **14f** afforded enantioenriched **15f** in 52% yield, as shown in Scheme 9.

We next tried to synthesize α-mycolic acid (**1**), which is a long fatty acid containing two cyclopropane rings in its saturated carbon chain, and which was initially isolated from *Mycobacterium Tuberculosis* in 1938.[7] It is known that mycolic acids produced by *Mycobacterium Tuberculosis* are a mixture of β-hydroxy acids. These acids contain at least one cyclopropane ring on a long, saturated carbon chain containing more than 40 carbons and possessing a branched alkyl chain at the α-position. The first total synthesis of α-mycolic acid was reported by Baird et al. in 2003,[17,21] where a Wittig reaction or Julia olefination and the subsequent diimide reduction of the



Scheme 10. Synthesis of meromycolate moiety **26** of α-mycolic acid.

resulting olefin moiety were employed to extend the saturated carbon chain of α-mycolic acid. In addition, for the extension of the carbon chain, multistep transformations of the reacting sites were required.

In contrast, the present method using the building blocks mentioned above requires only one step, the direct bromination of the siloxy group by Br_2-PPh_3, for the subsequent coupling reaction with Grignard reagents. In addition, by an additional transformation of the bromide to the corresponding Grignard reagent, the coupling reaction with alkyl halides could be conducted. Accordingly, we assembled the meromycolate moiety **26** of α-mycolic acid **1** by means of the present sequential coupling reaction of the building blocks (Scheme 10).

The cross-coupling reaction of building block **7** with octadecyl Grignard reagent in the presence of 3 mol% of $NiCl_2$ and 1 equiv of 1,3-butadiene in THF gave the corresponding coupling product **20** in 85% yield. The subsequent treatment of **20** with in situ generated Br_2PPh_3 in dichloromethane at room temperature afforded the corresponding bromide **21** in 88% yield. Next, we submitted bromide **21** to the coupling reaction with Grignard reagent **22** under the same catalytic conditions. The subsequent deprotection of the silyl group by TBAF in the same flask gave the desired product **23** in 56% yield. This somewhat low yield is probably due to the lower solubility of the long alkyl bromide **21** under the coupling reaction conditions. Indeed, the reaction mixture was a pale yellow suspension, and the yield of the coupling reaction gradually decreased as the alkyl chain of the bromides became longer.[22] In order to improve the yield, the reaction conditions were examined using bromide **21** and Grignard reagent **22**. When the reaction was conducted at an elevated reaction temperature (50 ºC) in the presence of $NiCl_2$ and 1,3-butadiene, the reaction mixture became a clear solution, and the yield increased to 74%. At 50 ºC, a copper/1-phenyl-1-propyne catalytic system[14b,c] yielded the coupling product **23** in 64% yield, although a cobalt/1,3-pentadiene catalytic system resulted in a lower yield (21%).[14d-f] In addition, when the corresponding fluoride was used instead of bromide **21**, the coupling product **23** was obtained in 65% yield by the copper/1-phenyl-1-propyne catalyst at 50 ºC.

Treatment of **23** with PPh_3, CBr_4, and imidazole in dichloromethane afforded the corresponding bromide **24** in 78% yield, which was then subjected to the Cu-catalyzed cross-coupling reaction with Grignard reagent **25**. The subsequent deprotection furnished meromycolate moiety **26** in 74% yield over two steps. From the cyclopropane-containing building block **7**, we constructed a C38 saturated hydrocarbon chain involving two cyclopropane rings in 32% total yield. Meromycolate moiety **26** is a key intermediate in Baird's total synthesis of α-mycolic acid **1**.[17]

Conclusion

Various CFAs were prepared by the $C(sp^3)$–$C(sp^3)$ cross-coupling reaction of cyclopropane-containing building blocks with alkyl Grignard reagents or alkyl bromides using a Ni/1,3-butadiene or a Cu/alkyne catalytic system, demonstrating the usefulness and versatility of these *cis*- and *trans*-cyclopropane building blocks for the assembly of CFAs. The present synthetic method constructed the saturated carbon frameworks directly, and constitutes a simpler route to CFAs than hitherto-known synthetic methods. The results reported herein, along with our previous work,[15] demonstrate that the iterative $C(sp^3)$–$C(sp^3)$ cross-coupling reaction of bifunctional building blocks is a powerful and straightforward synthetic tool to access fatty acids bearing various motifs, such as olefin and cyclopropane in their saturated carbon chain. The usefulness of the iterative $C(sp^3)$–$C(sp^3)$ cross-coupling reaction was also demonstrated by the formal total synthesis of a long fatty acid, α-mycolic acid.

Experimental Section

General Procedure for the Cross-Coupling Reaction of 7 with Alkyl Grignard Reagents and Following Bromination (Table 1)

A Schlenk tube containing **7** (876 mg, 3.0 mmol) and THF (1.0 mL) was added alkyl Grignard reagent (in THF, 6.0 mmol), 1,3-butadiene (13.5 mL as gas, 0.6 mmol), and $NiCl_2$ (3.9 mg, 1 mol%), successively, at –78 °C and stirred at 0 °C for 1 h. The reaction was carefully quenched by the addition of 1N HCl aq. (10 mL) and extracted by Et_2O (3 x 20 mL). The combined organic layer was dried over Na_2SO_4 and concentrated to obtain a crude product. The crude product was used for next step without further purification. A solution of PPh_3 (2.36 g, 9 mmol) in CH_2Cl_2 (30 mL) was added bromine until the color of bromine did not disappear. To this mixture, the crude product was added and stirred at rt. After 12 h, the mixture was added water (50 mL) and extracted by CH_2Cl_2 (3 x 30 mL). The organic layer was dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography afforded the corresponding product.

General Procedure for the Cross-Coupling Reaction of 13 with Bromoalkanoic Acid (Table 2)

A Schlenk tube containing Mg (49 mg, 2 mmol) was added THF (1 mL) and 1,2-dibromoethane (16 μL) to activate Mg followed by the slow addition of bromide **13** (1.0 mmol). The mixture was heated at 60 °C for 30 min. Another Schlenk tube containing bromoalkanoic acid (0.5 mmol), THF (0.5 mL), and NMP (50 μL) was cooled to –78 °C, added *t*BuMgCl (in THF, 0.5 mmol), and stirred at the same temperature for 10 min. The Schlenk tube containing Grignard reagent was cooled with a dry ice-EtOH bath and added 1,3-butadiene (11.2 mL, 0.5 mmol), the solution of magnesium bromoalkanoate via a cannula, and $NiCl_2$ (0.7 mg, 1 mol%), successively. The reaction mixture was stirred at 0 °C for 1 h and then quenched by 1N HCl aq. (5 mL). The product was extracted by Et_2O (3 x 10 mL), dried over Na_2SO_4, and purified by silica gel column chromatography.

General Procedure for the Cross-Coupling Reaction of 11 with Alkyl Grignard Reagents and Following Bromination (Scheme 8 and Table 3)

A Schlenk tube containing **11** (876 mg, 3.0 mmol) and THF (1.0 mL) was added alkyl Grignard reagent (in THF, 6.0 mmol), 1,3-butadiene (13.5 mL as gas, 0.6 mmol), and $NiCl_2$ (3.9 mg, 1 mol%), successively, at –78 °C and stirred at 25 °C for 1 h. The reaction was carefully quenched by the addition of 1N HCl aq. (10 mL) and extracted by Et_2O (3 x 20 mL). The combined organic layer was dried over Na_2SO_4 and concentrated to obtain a crude product. The crude product was used for next step without further purification. A solution of PPh_3 (2.36 g, 9.0 mmol) in CH_2Cl_2 (30 mL) was added bromine until the color of bromine did not disappear. To this mixture, the crude product was added and stirred at rt. After 12 h, the mixture was added water (50 mL) and extracted by CH_2Cl_2 (3 x 30 mL). The organic layer was dried over Na_2SO_4 and concentrated. Purification by silica gel column chromatography afforded the corresponding product.

General Procedure for the Cross-Coupling Reaction of 16 with Grignard Reagent 17 and Following Deprotection (Scheme 8 and Table 3)

A Schlenk tube containing Mg (49 mg, 2 mmol) was added THF (1 mL) and 1,2-dibromoethane (16 μL) to activate Mg followed by the slow addition of a ω-(*tert*-butyldimethylsiloxy)alkylbromide (1.0 mmol: For the synthesis of this compound, see SI). The mixture was heated at 60 °C for 30 min and then cooled to –78 °C and added **16** (0.5 mmol), 1,3-butadiene (11.2 mL, 0.5 mmol), and $NiCl_2$ (0.7 mg, 1 mol%). After stirring at 0 °C for 1 h, the reaction was quenched by adding 1N HCl aq. (5 mL). The product was extracted by Et_2O (3 x 20 mL), dried over Na_2SO_4, and concentrated in vacuo. To the crude product, TBAF (1 M in THF, 1.5 mL, 1.5 mmol) was added and stirred at rt for 3 h. The reaction mixture was diluted with water (10 mL) and extracted by Et_2O (3 x 20 mL). The organic layer was dried over Na_2SO_4, concentrated, and purified by silica gel column chromatography.

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UPDATE

Synthesis of Cyclopropane Fatty Acids by C(sp^3)–C(sp^3) Cross-coupling Reaction and Formal Synthesis of α-Mycolic Acid

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