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Recent advances of carbonyl olefination *via* McMurry coupling reaction

Anthony Bongso, Robby Roswanda * and Yana Maolana Syah

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McMurry coupling reaction utilizes the low-valent titanium reagents and carbonyl compounds to produce olefins. The wide synthetic application of McMurry reagents in intermolecular and intramolecular coupling reactions, tandem coupling reactions, and keto ester coupling reactions of carbonyl compounds for the last five years have been reviewed. The resulting coupling reaction produces natural and non-natural products, including strained olefins and unusual molecules as a candidate for nanomaterials, pharmaceuticals, electronic materials, and so forth. The advantages, scope, and limitations along with the improvement of the McMurry coupling reaction, including the addition of high functional group compatibility, McMurry reagents substitution, and several other treatments, have also been discussed.

1. Introduction

In organic synthesis, the formation of olefin is essential to create numerous natural products and non-natural products that can be applied in health, industry, functional materials, *etc.* Several methods continue to be explored and developed in order to obtain an olefination reaction that is able to control the stereoselectivity, regioselectivity, and chemoselectivity of the reaction. Some of the methods are Horner–Wadsworth–Emmons reaction, Wittig reaction, Julia–Kocienski olefination, and Tebbe olefination.[1,2] Other olefination reactions on a catalytic scale that are worth mentioning, such as olefin metathesis (*e.g.*, Grubbs metathesis) and cross-coupling reactions (*e.g.*, Heck reaction), continue to be known, studied and developed, and are still widely applied.

In 1973, the formation of olefin *via* reductive coupling of carbonyl compounds using low-valent titanium was discovered by Tyrlik with Wolochowicz and Mukaiyama *et al.*[3,4] Mukaiyama *et al.* reported the reductive coupling of ketones and aromatic aldehyde by utilizing the $TiCl_4$–Zn system. The result of the reductive coupling of acetophenone and benzaldehyde was successful conversion into olefin and pinacol.[4] Due to the formation of pinacol, Mukaiyama *et al.* suggested that the metallopinacolate occurs as an intermediate during the reductive coupling reaction. On the contrary, Tyrlik and Wolochowicz proposed that tetramethylene was obtained through carbene species that occur during the deoxygenation of acetone.[3] Due to the absence of by-products from the reductive coupling reaction, the presence of intermediates prior to the formation of carbene species cannot be ascertained. The proposed mechanisms of carbonyl olefination *via* reductive coupling by Tyrlik with Wolochowicz and Mukaiyama *et al.* can be seen in the (Fig. 1). Later in 1974, another formation of olefin *via* reductive coupling of carbonyl compounds, including aliphatic substrates has been developed by McMurry and Fleming.[5] This reaction, known as McMurry reaction, utilizes low-valent titanium reagents and carbonyl compounds to produce olefins. In this experiment, McMurry and Fleming introduced the $TiCl_3$/$LiAH_4$ system (known as McMurry reagent) which works efficiently in reductive coupling reactions involving aromatic and aliphatic ketones. The success of McMurry and Fleming in isolating pinacol supports the proposed mechanism by Mukaiyama *et al.* which suggested the presence of metallopinacolate as an intermediate in the reductive coupling reaction.

Continuing the previous research, McMurry and coworkers began to improve the procedures for the reductive coupling reaction. Various McMurry system, namely $TiCl_3$/K,[6,7] $TiCl_3$/Li,[7]

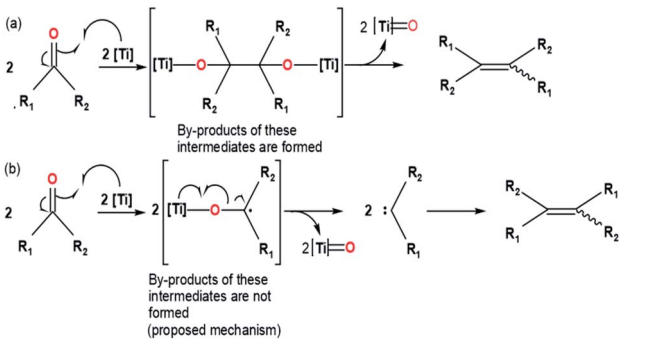

Fig. 1 McMurry coupling involving a metallopinacolate intermediate mechanism proposed by Mukaiyama *et al.* (a) and by Tyrlik and Wolochowicz (b).[3,4]

Organic Chemistry Division, Faculty of Mathematics and Natural Sciences, Institut Teknologi Bandung, Jalan Ganesha 10, Bandung 40132, Indonesia. E-mail: r.roswanda@itb.ac.id

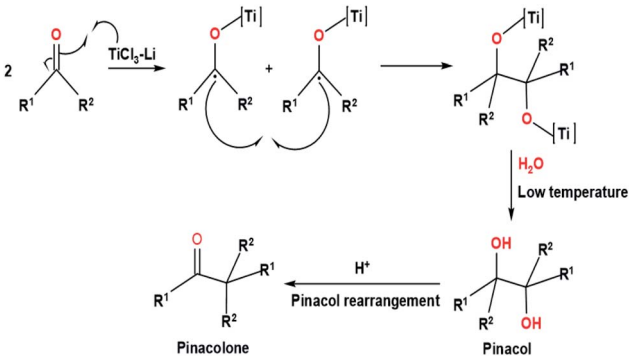

Fig. 2 Formation and rearrangement of pinacol as a side product.

and $TiCl_3(DME)_{1,5}$/Zn–Cu[8] were tested to find the best system for preparing the low-valence titanium reagent. Other systems were also tested and reported by another researcher, such as $TiCl_4$/Zn/pyridine,[9] $TiCl_3/C_8K$,[10,11] $TiCl_4/C_8K$/pyridine,[10] and $TiCl_4$/Mg (Hg)/pyridine.[10] Various uses of organometals other than titanium for carbonyl coupling reactions such as zirconium, hafnium, niobium, tantalum, chromium, molybdenum, tungsten, iron, manganese, rhenium, lanthanide, and actinide groups have also been explored and briefly summarized by Kahn and Rieke.[12] In addition, the scope and limitations of the McMurry reaction such as the compatibility of functional groups with low-valence titanium and some of its synthetic applications have also been reported and briefly summarized by McMurry.[13]

Nowadays, McMurry coupling reaction is widely utilized in the field of biochemistry, materials science, organic synthesis, and organometallic synthesis. A numerous carbonyl substrates including aldehyde, keto-esters, acylsilanes, oxoamides can be coupled efficiently, *via* intermolecular or intramolecular McMurry coupling reaction to construct several natural products and non-natural products including strained olefins and unusual molecules. This type of reaction has been applied in the synthesis of loratadine as an antihistamine drug to relieve symptoms of allergies, prevent motion sickness and treatment for insomnia, the synthesis of tamoxifen as an antitumor agent.[14] McMurry coupling reaction has also been used to create material such as polycyclic aromatic hydrocarbons (PAHs) as a candidate of light emitting diodes, transistors, and solar cells.[15]

However, the potential of McMurry coupling reaction is now less utilized due to a statistical mixtures of products specifically an intermolecular reaction involving two different carbonyl compounds, non-stereospecific product, formation of pinacol as a side product,[16] and undesirable pinacol rearrangement (Fig. 2). McMurry coupling reaction is also limited by substrate's structural requirement such as aryl ketones with aryl ketones, aryl ketones with aliphatic ketones, diaryl ketones with diaryl ketones. Moreover, this reaction also requires prolonged time for substrate deoxygenation and high temperatures. Therefore, many things still need to be improved from the McMurry coupling reaction. Another problem related to the McMurry reaction that is important to note is the stoichiometric amount of titanium salts and reductants used in reaction, resulting a lot of waste. This stoichiometric problem followed by the extreme conditions of McMurry reaction prompted the researchers to develop transition-metal-catalyzed deoxygenative coupling reactions under mild conditions. In 1995, Fürstner and Hupperts succeeded in designing a catalytic deoxygenation coupling reaction using the $TiCl_3$/Zn system with the addition of excess chlorosilane (*e.g.*, (TMS)Cl, $(EtO)_3SiCl$, $(i\text{-}Pr)_3SiCl$, $ClSi(Me)_2\text{-}CH_2CH_2Si(Me)_2Cl$).[17] This encounter is crucial considering the addition of chlorosilane can reduce the amount of stoichiometric titanium salt used to 5–10% mol with a high-yield synthesis.[17] Excess chlorosilane can also be removed easily *in vacuo*, so complex workup of the reaction mixtures is not necessary. The Cp_2TiCl_2 catalytic system was also applied by Diéguez *et al.* in carrying out carbonyl olefination reactions, 1,2-diol deoxygenation, and alcohol deoxygenation.[18] Other catalytic system such as $TiCl_4$/Yb,[19] $TiCl_4$/Sm,[19] $TiCl_4$/Dy,[19] $[Ir(FCF_3ppy)_2dtbpy]PF_6/B_2pin_2$,[20] $[Rh_2(OAc)_4]$,[21] and other organometals which require conversion of carbonyl into hydrazone have also been explored and briefly summarized by Asako and Ilies.[22]

Many reviews have been discussing the latest in McMurry reaction such as the 2013 review by Takeda in Organic Reactions and the book "Modern Carbonyl Olefination: Methods and Applications".[23,24] In this review, we are summarizing and analyze the information, for the latest five years, related to the McMurry reaction in several reviews, which consists of the type of reaction, general procedure, reagents, functional group compatibility, additives, and its application in the synthesis of natural and non-natural products. In addition, we will also discuss the advantages and disadvantages of the McMurry reaction, also the treatments to minimize the drawbacks of the McMurry reaction.

2. Coupling reagents and general procedure

2.1 Coupling reagents

2.1.1 Substrates. In the McMurry reaction, the substrates must contain one or more carbonyl functional groups. Numerous carbonyl substrates such as aldehyde, ketone, oxoamide, acylsilanes, conjugated enones, acyloin, and keto-ester can be coupled to form olefins. The addition of functional groups to the substrates such as aryl, alcohol, alkene, halide, ester, ether, alkyl, phospholes, amine, sulfide, and others could either activate or deactivate the adjacent carbonyl that will be discussed in the latter section.[13]

2.1.2 Sources of low-valent metals. Low-valent metals have a predominant role in the McMurry reaction. The substrate coupling was induced by a single electron transfer from low-valent metal to the carbonyl groups. Due to the high reducing potential and strong oxophilicity of low-valent metals, the metal ion causes the carbonyl groups on the substrate to move closer to one another and easily deoxygenated. The common low-valent metal in the McMurry reaction is zero-valent titanium. Zero-valent titanium was prepared by reducing titanium

tetrachloride or titanium trichloride with strong reducing agents. Several metals have been explored in the McMurry coupling reaction. Some of the metals are vanadium,[25] tungsten,[26,27] molybdenum,[27] niobium,[28] and lithium.[29] In 1982, Geise *et al.* reported using cobalt, nickel, iron, copper, chromium, zinc, manganese, tin, hafnium, and tantalum in benzophenone coupling experiments with lithium aluminum hydride as a reducing agent shows negative results.[29] Recently, the group of Nakamura has shown that active low-valent metal was effectively prepared by reducing hafnium tetrachloride and zirconium tetrachloride with zinc dust for the coupling of two aryl ketones molecules.[30] Additionally, Moxter *et al.* has successfully performed the "Sila-McMurry" coupling reaction using disilicon hexachloride in benzene-d_6 solution.[31]

2.1.3 Solvents. Tetrahydrofuran (THF) is the most widely used solvent in McMurry reaction because of its ability to dissolve intermediate pinacolate complexes, facilitate the electron transfer process, and maintain its form without being reduced under the McMurry reaction conditions. Another solvent as a substitute to THF solvent is dimethoxyethane (DME). DME is often used in organometallic reactions, due to its ability to form bidentate ligands with metal cations. This solvent is suitable for high-temperature reactions. McMurry has reviewed the reduction of $TiCl_3(DME)_{1.5}$ with Zn–Cu generates active zero-valent titanium.[13]

2.1.4 Reducing agents. Activated zinc metal or zinc-copper is a common reducing agent used for McMurry reaction. Zinc-copper has been preferred because copper can enhance the reactivity of zinc by weakening the zinc–zinc bond. Several other reducing agents that have been used are magnesium-mercury amalgam,[32] lithium aluminum hydride,[32] potassium metal,[33] and lithium metal.[33] The use of potassium or lithium metal has rarely been applied in the McMurry reaction due to its flammable and explosive characteristics. Based on the research conducted by Harit and Ramesh regarding the synthesis of aminocylitols *via* pinacol coupling reaction, the use of magnesium–mercury amalgam as a reducing agent in THF was unsuccessful, whereas lithium aluminum hydride in DME produced aminocylitols with 10% yields. By using the zinc–copper couple in THF, the product was successfully synthesized with 63% yields.[32]

2.1.5 Other functional reagents. Additional compatible reagents are used to enhance the carbonyl olefination process. Pyridine is used as a base to neutralize excess acid from metal ions. Potassium carbonate or sodium carbonate and HCl are used as a quenching reagent to deactivate any unreacted reagents.

2.2 General procedure

The McMurry reaction is completed in two steps: reduction of $TiCl_4$ to form low-valent titanium and deoxygenation of carbonyl substrates. Under an inert atmosphere, a suspension of low-valent titanium was prepared from the dropwise injection of $TiCl_4$ into a two or three-necked round-bottomed flask containing an amount of reducing agents in a dry THF or DME at 0 °C. The mixture was refluxed for several hours. After cooling the mixture to 0 °C up to −5 °C, the substrates and a small amount of pyridine were added to the reaction mixture and refluxed for several hours or up to overnight. The solution was cooled at room temperature and quenched by the dropwise addition of a quenching reagent. Furthermore, the product can be purified by extraction, column chromatography, or recrystallization.

3. Reaction mechanism

In general, two reaction steps occur in the McMurry coupling reaction (Fig. 3). The first step is carbonyl substrates reduction by a single electron transfer from titanium to produce ketyl radical compounds that can be dimerized to form intermediate pinacols (metallopinacolate). By decreasing the reaction temperature from reflux to 0 °C, the intermediate pinacols can be isolated in a high yield.[13] The second step involves the deoxygenation of metallopinacolate to form olefins by maintaining the reflux temperature.

Although the McMurry coupling reaction was discovered more than four decades ago, only a few details regarding the mechanism of the McMurry coupling reaction were known. By this time, the mechanism of the McMurry reaction can only be explained through a hypothetical approach. Four hypothetical pathways consist of paths A_1, A_2, B, and C related to McMurrys's reaction mechanism have been illustrated in Fig. 4.[34]

In path A, the metallopinacolate forms a five-membered ring structure with two oxygen atoms bound to the same zero-valent titanium. The homolytic cleavage of C–O bonds in metallopinacolate, oxidation of titanium, and the formation of the C–C bond were carried out simultaneously through the concerted process (path A_1) or non-concerted process (path A_2). The difference between path A_1 and path A_2 lies in the homolytic cleavage process of C–O bonds in metallopinacolate. In path A_1, the two C–O bonds broke concurrently, whereas path A_2 describes the cleavage of two C–O bonds at different times. Hypothetically, path A is a regioselective reaction due to the presence of a titanium ion bonded to two oxygen atoms. However, based on the experiment reported by McMurry *et al.*, shows that the coupling of pentanal to form 5-decene (70% *trans*, 30% *cis*) *via* McMurry coupling

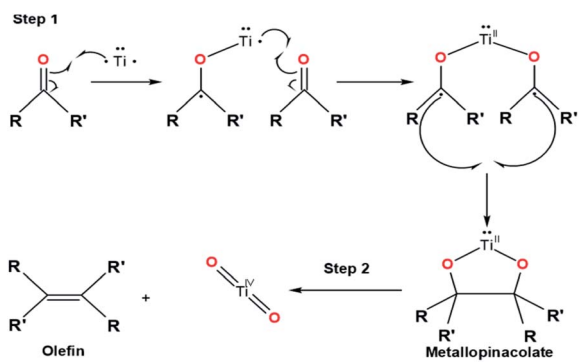

Fig. 3 General steps in the McMurry coupling reaction.

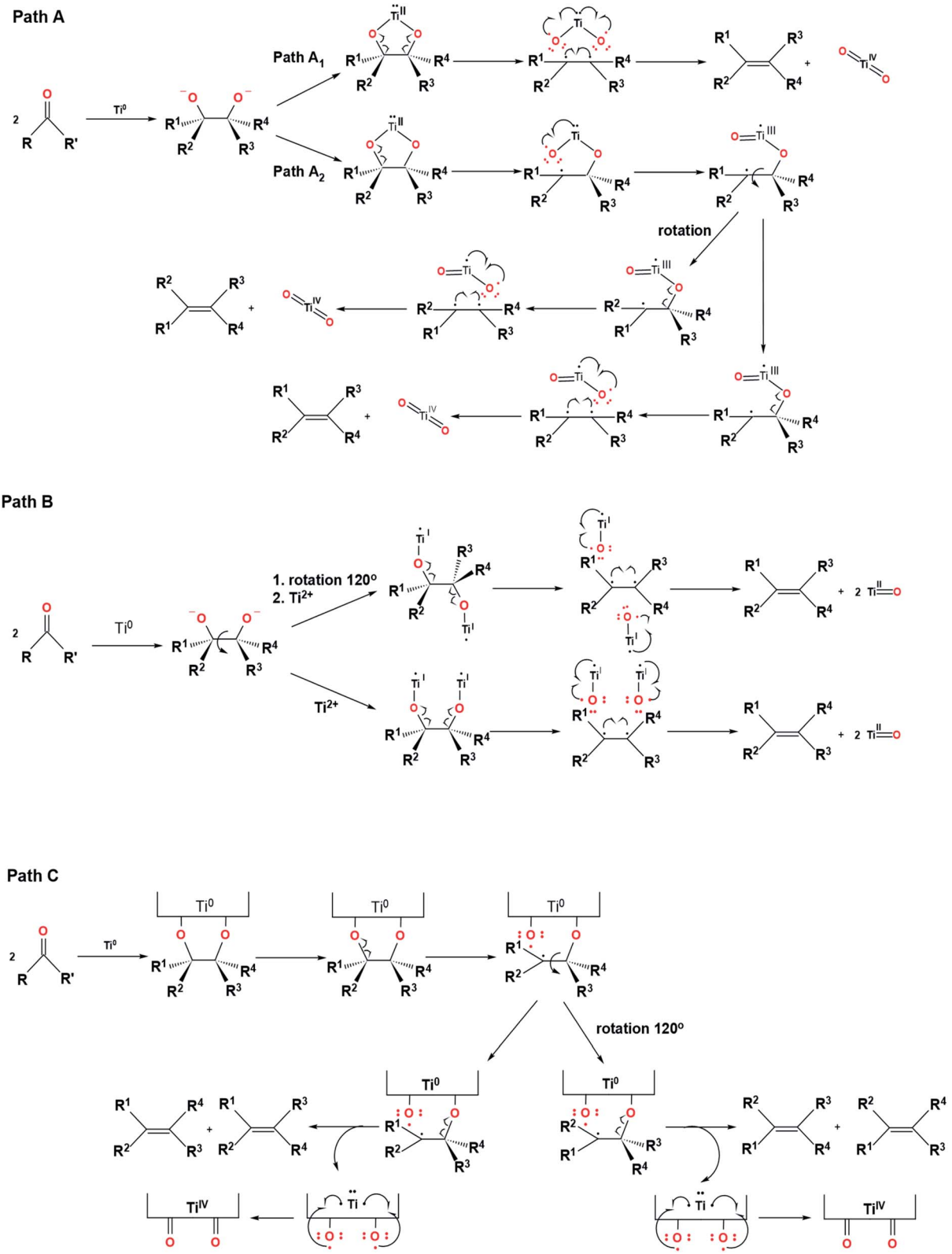

Fig. 4 Four hypothetical pathways related to McMurry's reaction mechanism.[34]

reaction is not a regioselective reaction (Fig. 5).[7] Hence, another path to describe the McMurry coupling reaction is needed.

In path B, the two oxygen atoms in the intermediate pinacols bonded to different titanium. This path does not involve the five-membered ring structure in the intermediate. The

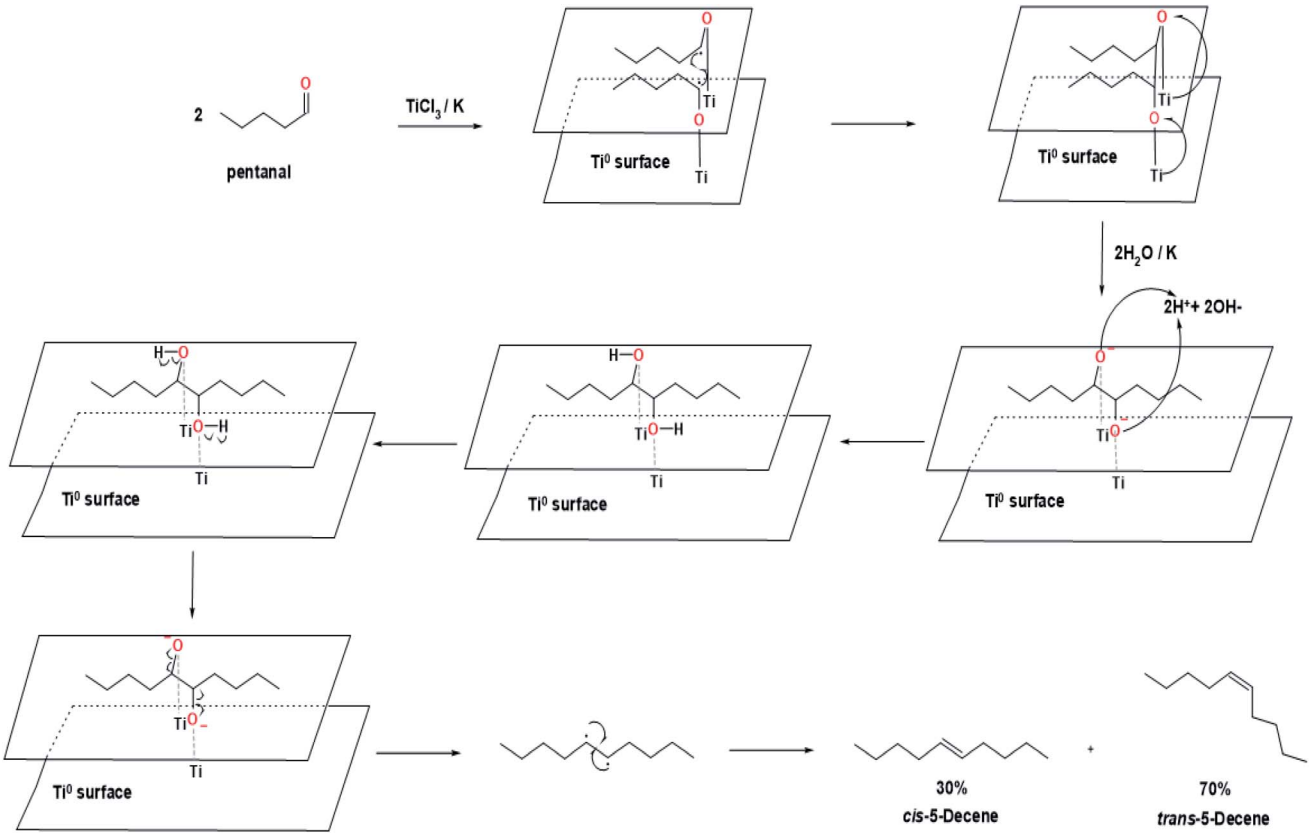

Fig. 5 Proposed mechanism for the synthesis of *cis*-5-decene and *trans*-5-decene from pentanal.[7]

homolytic cleavage of C–O bonds in path B adopts a non-concerted process. The rotation of C–C bonds occurred due to the high-density electrons in the σ bond between two carbon nuclei. In 1978, McMurry *et al.* also reported an experiment related to the synthesizing of 1,2,3,4,5,6,7,8-octahydronaphthalene from *cis*-9,10-decalindiol and *trans*-9,10-decalindiol *via* intramolecular reaction using $TiCl_3$/K system to determine the feasibility of path B (Fig. 6).[7] The use of *cis*-9,10-decalindiol as a substrate to produce 1,2,3,4,5,6,7,8-octahydronaphthalene was successful with 80% yields, while *trans*-9,10-decalindiol did not produce 1,2,3,4,5,6,7,8-octahydronaphthalene due to the lack of energy to cleave the carbon and oxygen bonds.[7] These results undermine the plausibility of path B in explaining the McMurry coupling reaction mechanism.

The last hypothetical pathway to explain the McMurry coupling reaction mechanism is path C. In path C, the two oxygen atoms from metallopinacolate bonded to the titanium(0) surface, which adopts heterogeneous catalysis process. The difference between path C and path A lies in the number of titanium involved in the reaction. Path C involves two titanium atoms bonded to two oxygen atoms without forming a five-ring

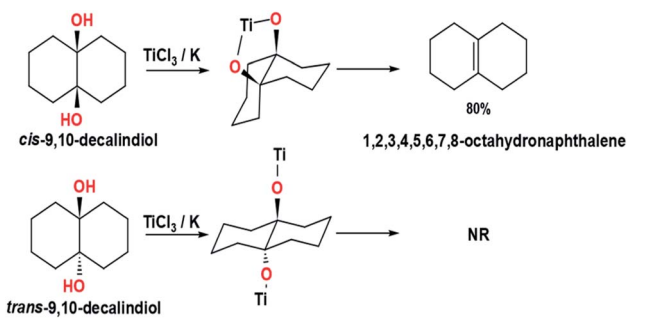

Fig. 6 Synthesis 1,2,3,4,5,6,7,8-octahydronaphthalene from *cis*-9,10-decalindiol (top) and *trans*-9,10-decalindiol (bottom).[7]

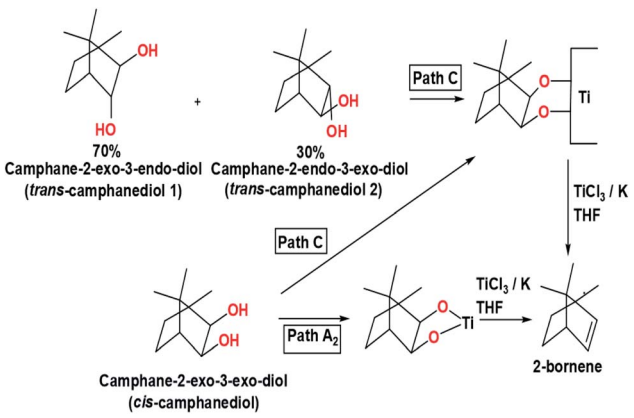

Fig. 7 Synthesis of 2-bornene from *cis*-camphanediol and *trans*-camphanediol.[7]

Table 1 Result of synthesis 2-bornene from *cis*-camphanediol and *trans*-camphanediol[7]

		Yield of 2-bornene (%)	
Run	Time (h)	*cis*-Camphanediol	*trans*-Camphanediol 1 + *trans*-camphanediol 2 (70 : 30)
1	0.5	51	29
2	1	76	33
3	5	81	60

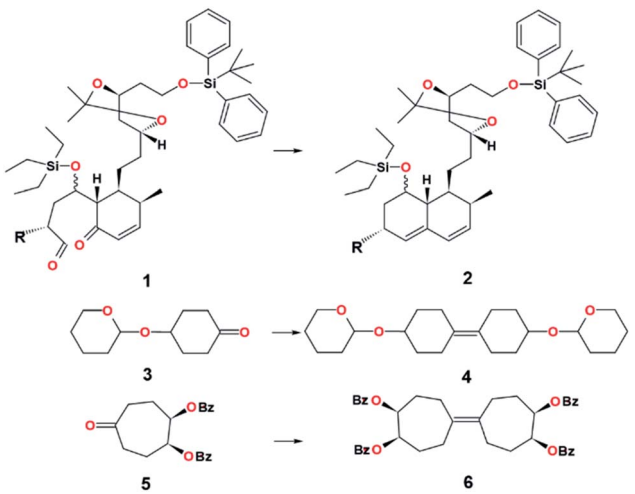

Fig. 8 McMurry coupling reaction of carbonyl substrate containing acetal groups.

intermediate, but the Ti–O bonds could break simultaneously. Path C also allows two oxygen atoms to bind to different titanium surfaces. This flexible mechanism is similar to a combination of path A and path B, which cover each other's shortcomings. The isomeric reaction mechanism of decalindiol to produce octahydronaphthalene can be explained through path A_2 and path C. In 1978, McMurry *et al.* also mentioned an experiment related to the synthesis of 2-bornene *via* reductive coupling of *cis*-camphanediol and a 70 : 30 mixtures of *trans*-camphanediol 1 with *trans*-camphanediol 2 using $TiCl_3$/K in THF to determine which pathway is more feasible to describe the McMurry coupling reaction mechanism (Fig. 7).[7] If the reaction involves metallopinacolate intermediates with a five-membered ring structure (path A_2), the reduction of *cis*-camphanediol will be faster than the reduction of *trans*-camphanediol. Meanwhile, if the reaction goes through path C, both *cis*- and *trans*-camphanediol will reduced at equal rates. Based on the experimental data in Table 1 shows the *cis*-camphanediols and *trans*-camphanediols were reduced at approximately equal rates.[7] Therefore, the McMurry coupling reaction is more likely to occur *via* a heterogeneous catalysis process on an active titanium surface (path C).

4. Functional group compatibilities

When carrying out the McMurry coupling reaction, the selection of substrates-containing functional groups bonded to the carbonyl needs to be considered. Some functional groups are incompatible with the McMurry reaction due to the ability of low-valent titanium to reduce certain functional groups. Characterization of olefin products can be performed to determine whether the functional group has been transformed into another group during the reaction process. This section discusses several functional groups classified as compatible, semi-compatible, and incompatible with the McMurry coupling reaction.

4.1 Compatible functional groups

Functional groups that are compatible with the McMurry coupling reaction is a group that is not easily reduced and have an ability to maintain its form under reaction conditions.

4.1.1 Acetal. Acetals are prone to hydrolysis in acidic conditions. This could be problematic since metal ions contribute to the acidic atmosphere in the reaction can cause the acetal groups to be hydrolyzed during workup. The addition of aqueous sodium carbonate, aqueous ammonia, pyridine, or triethylamine could prevent the hydrolysis process by keeping the reaction in an alkaline atmosphere. Several experiments have applied the McMurry coupling reaction in combining the acetal functional group substrate (Fig. 8), including the synthesis of olefin, **2**, through the intramolecular coupling reaction of carbonyl substrate, **1**, with the presence of acetal (Table 2).[11] Another unpublished experiment conducted by McMurry and Matz showed that tetrahydropyran ether, **4**, were obtained from the intermolecular coupling of two acetals, **3**.[13] Moreover, Sander and Dehmlow successfully synthesized 1-(*cis*-4′,5′-dihydroxycycloheptylidene)-*cis*-4,5-dihydroxycycloheptane, **6**, through McMurry coupling of the *cis*-4,5-dibenzyloxycycloheptanone compound, **5**.[35]

4.1.2 Alcohol (saturated alcohol complex and some aromatic alcohol). Some experiments have tested the compatibility of the alcohol groups in the McMurry reaction (Fig. 9). Alcohol groups such as saturated alcohols for large molecules or common aromatic alcohols are inert to low-valent titanium. Saturated alcohol such as cholesterol, **7**, cannot be coupled *via*

Table 2 McMurry coupling reaction of carbonyl substrate containing acetal groups

Substrate	Product	Source of metal	Reducing agent	Solvent	Yield (%)	Ref.
1	**2**	$TiCl_3$	C_8K	DME	86	11
3	**4**	$TiCl_3(DME)_{1.5}$	Zn–Cu	DME	97	13
5	**6**	$TiCl_3$	$LiAlH_4$	THF	98	35

Table 3 McMurry coupling reaction of carbonyl substrate containing saturated alcohol and aromatic alcohol groups

Substrate	Product	Source of metal	Reducing agent	Solvent	Yield (%)	Ref.
7	NR	LVT	—	THF	—	13
8 & **9**	**10**	$TiCl_4$	Zn	THF	91	36
11 & **12**	**13**	$TiCl_4$	Zn	THF	51[a]	37
14 & **15**	**16**	$TiCl_4$	Zn	THF	30	38

[a] The measured yield was the yield after the precursor undergo alkylation with $Cl(CH_2)_nNMe_2$ with the addition of NaOH, acetone, and HCl.

McMurry reactions due to the steric effect that makes the oxygen atoms hardly interact with the low-valent titanium surface.[13] In 2003, Yu and Forman successfully synthesized (*E*,*Z*)-4-hydroxytamoxifen, **10**, through the McMurry coupling reaction (Table 3).[36] The *E* and *Z* isomers were separated by a selective crystallization method to obtain (*Z*)-4-hydroxytamoxifen as a candidate of estrogen receptor modulator. The hydroxy complex, **13**, was successfully synthesized by Top *et al.* as a precursor in the manufacture of hydroxyferrocifen compounds or ferrocifen metabolites.[37] Another ferrocenyl analogs, namely 3-ferrocenyl-4-(4-hydroxyphenyl)-hex-3-ene, **16**, have also been synthesized by coupling propionylferrocene, **14**, with 4-hydroxypropiophenone, **15**, *via* McMurry reaction.[38]

4.1.3 Halide. The halide functional groups are the groups that are rich in electrons. Their electron-rich nature and compliance with the octet rule make the halide groups less likely to accept electrons from the low-valent titanium. Generally, organohalides are not reduced by low-valent titanium. For example, McMurry couplings of chloropropionylferrocene, **17**, with 4,4′-dihydroxybenzophenone, **18**, give the corresponding ClFcdiOH, **19**.[38] The intermolecular coupling *via* McMurry reaction of 4-bromobenzophenone, **20**, yields 1,2-bis(4-bromophenyl)-1,2-diphenylethenes, **21**.[39] Synthesis 1,2-di(4-bromophenyl)-1,2-di(1,3,5-triphenylbenzene-4′-yl)ethylene, **23**, from 4-bromo-4'-[(3,5-diphenyl)phenyl]benzophenone, **22**, *via* McMurry coupling reaction has been successfully carried out.[40] Additionally, synthesis of 1,6-dihalo-1,3,5-hexatrienes, **25**, can also be obtained from the β-haloacrylaldehydes derivatives, **24**.[41] Another McMurry reaction was shown in the coupling of 2-iodobenzaldehyde, **26**, to produce compound **27** with 55% yield (Table 4).[42] Based on the information obtained through the literature shows that the halide functional groups in the product remain the same as the functional groups on the substrate (Fig. 10).

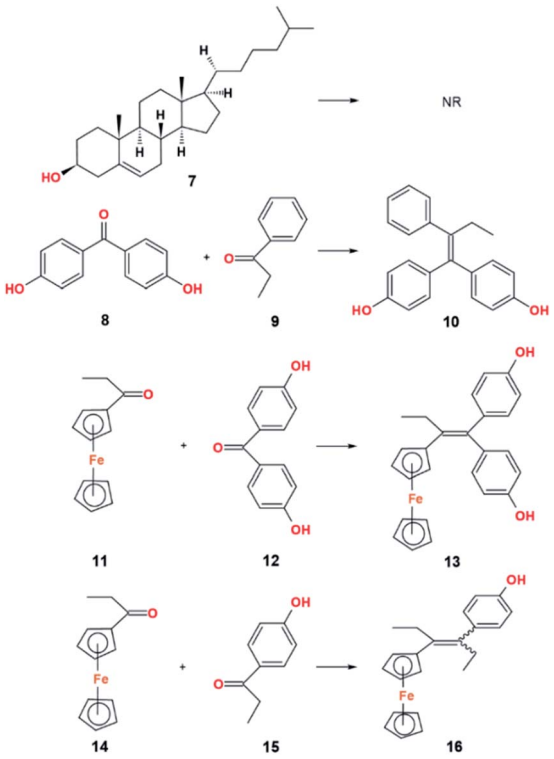

Fig. 9 McMurry coupling reation of carbonyl substrate containing saturated alcohol and aromatic alcohol groups.

4.1.4 Substituted silane. Substituted silanes such as vinyl and alkyl silane do not react with low-valent titanium (Fig. 11). In 1994, Roth and Horn reported that the intermolecular coupling of the tetraalkylsilane substrate, **28**, yields an olefin containing two tetraalkylsilane groups, **29**.[43] Based on the experiment conducted by Disanavaka and Weedon, substituted silane compounds, **31**, were successfully synthesized through the intramolecular reaction of, **30**.[44] The results showed that the silane product did not undergo any further transformation under reaction conditions. The reductive coupling of bifunctional aldehyde, **33**, has also been performed by Paquette *et al.* to produce *trans*-1,2-bis[1-(trimethylsilyl)cyclopropyl]ethylene, **32**.[45] The first intermolecular and intramolecular McMurry coupling reaction of aroyltrimethylsilanes and *bis*-aroylsilane, **34** and **36**, to produce substituted 1,2-bis(trimethylsilyl)ethene derivatives, **35** and **37**, has also been performed successfully by Fürstner *et al.*[46] The stability of substituted silane under reaction conditions provides an opportunity to synthesize olefins containing substituted silane groups through McMurry coupling reactions (Table 5).

4.1.5 Sulfide and thiophene. The compatibility of the sulfide group is represented by the coupling products, **39**, of diketo-sulfides, **38**, *via* intramolecular McMurry coupling reaction (Table 6).[47] Other experiments have involved thiophene groups coupling reactions to synthesize various olefins. For

Table 4 McMurry coupling reaction of carbonyl substrate containing halide groups

Substrate	Product	Source of metal	Reducing agent	Solvent	Yield (%)	Ref.
17 & **18**	**19**	$TiCl_4$	Zn	THF	47	38
20	**21**	$TiCl_3$	$LiAlH_4$	THF	73	39
22	**23**	$TiCl_4$	Zn	THF	24	40
24	**25**	$TiCl_4$	Zn	DME	79	41
26	**27**	$TiCl_4$	Zn	THF	55	42

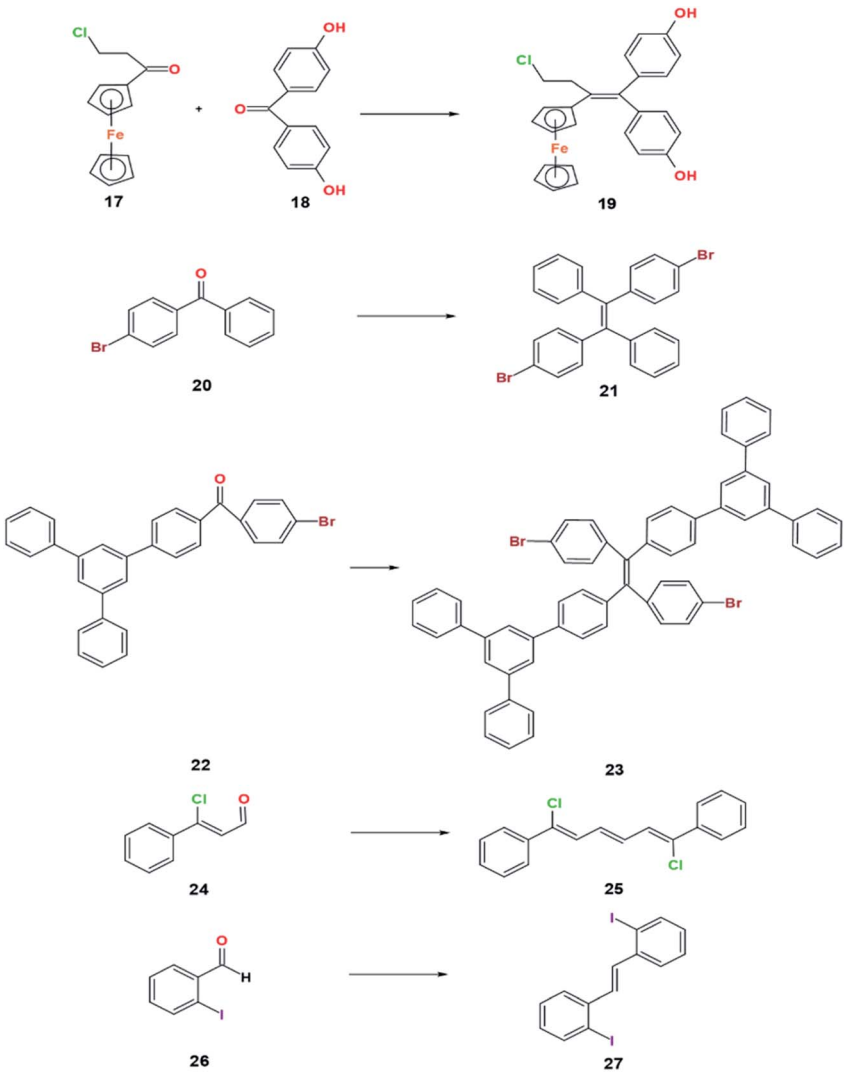

Fig. 10 McMurry coupling reaction of carbonyl substrate containing halide groups.

example, the dimer thienylenevinylene or 1,6-dithienylhexa-1,3,5-trienes, **42a–b** and **43**, were obtained through McMurry coupling of conjugated ketones, **40a–b** and **41**.[48] Additionally, DTEs or bridged dithienylethylenes with methyl substituents, **45**, can be obtained through the intermolecular reductive coupling of 4-methyl-4,5-dihydro-6*H*-cyclopenta[*b*]thiophen-6-one, **44**.[49] All these reactions have been illustrated in Fig. 12.

4.1.6 Ether. The compatibility of ether with the McMurry reaction can be depicted by the coupling products, **47**, from diether substrate, **46**.[50] Additionally, McMurry coupling of two calixanthone, **48**, was successfully performed by Agbaria and Biali to form dixanthylene, **49**.[51] The results of both experiments (Fig. 13) show that the ether groups are inert to low-valent titanium (Table 7).

4.1.7 Phospholes. Until recently, the application of the coupling reaction of carbonyl substrates containing phosphorus groups *via* the McMurry reaction was quite rare. The only experiments showing that phosphole is compatible under McMurry conditions (Fig. 14) are the synthesis of 1,2-bis(phosphacymantrenyl)alkenes, **51**, from McMurry coupling of 2-acylphosphacymantrenes, **50**,[52] and 1,2-bis(2-phospholyl) alkenes, **53**, from trifunctional substrates, **52** (Table 8).[53]

4.2 Semi-compatible functional groups

All the semi-compatible groups can be reduced slowly by low-valent titanium. Its resistance to low-valent titanium depends on the reaction conditions that can be adjusted by increasing or decreasing the reaction time, diluting, concentrating the mixture, or increasing the reaction temperature.

4.2.1 Amide. The compatibility of the amide functional group has been depicted in Fig. 15. The transformation of amide groups can be prevented by not extending the reaction time and not utilizing $LiAlH_4$ as a reducing agent during the coupling reaction. In 1985, Seijas *et al.* successfully applied the McMurry reaction in coupling substrates containing amide groups, namely synthesis of stilbene derivatives, **56**, from urethane, **54**, and benzaldehyde, **55**.[54] Moreover, McMurry

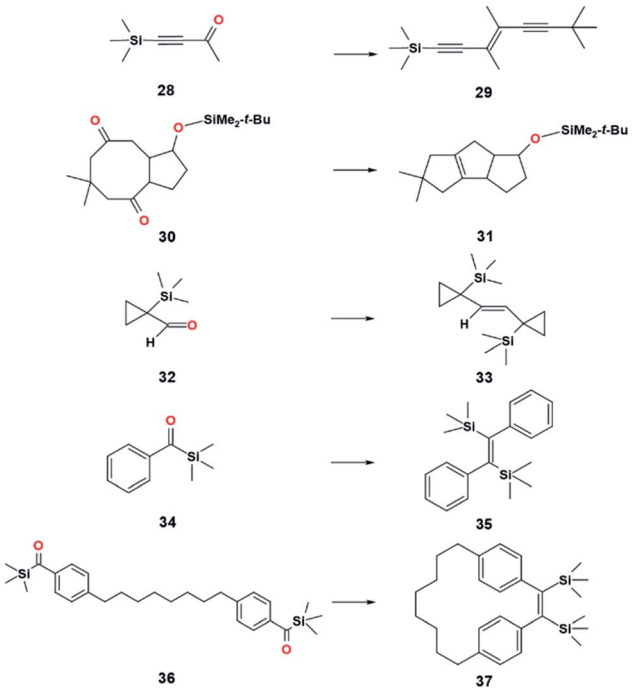

Fig. 11 McMurry coupling reaction of carbonyl substrate containing substituted silane groups.

Table 5 McMurry coupling reaction of carbonyl substrate containing substituted silane groups

Substrate	Product	Source of metal	Reducing agent	Solvent	Yield (%)	Ref.
28	**29**	$TiCl_4$	Zn	THF	41	43
30	**31**	$TiCl_3$	K	THF	38	44
32	**33**	$TiCl_3$	Li	DME	53	45
34	**35**	$TiCl_3$	Na on Al_2O_3	DME	67	46
36	**37**	$TiCl_3$	Na on Al_2O_3	DME	49	46

coupling of amide substrates, **57**, has also been performed to produce 11-indenoisoquinolines, **59** (Table 9).[55]

Although some experiments have demonstrated the resistance of the amide group to the McMurry reaction conditions, Fürstner *et al.* has reported the transformation of oxoamide, **60** and **62**, to produce various indole and pyrrole derivatives, **61** and **63**, *via* intramolecular coupling reaction.[56,57] Aside from synthesizing non-natural compounds, McMurry coupling of amide substrates has also been applied to synthesize biologically active compounds such as (+)-aristoteline, **65**, as a relaxation-inducing agent,[58] salvadoricine, **67**, as an antibiotic and antiseptic agent in *Salvadora persica*,[59] zindoxifene analogs, **69**, as an anti-cancer agent,[60] and camalexin, **71**, as an anti-bacterial and anti-pathogenic agent in *Arabidopsis thaliana*.[61] Amide cyclization through the McMurry reaction is also applied in the synthesis of certain materials, **73** and **75**, to produce seco-fascaplysin, which belongs to the sponge *Fascaplysinopsis reticulata* and indolopyridocolines that can be found in the bark of *Gonioma kamassi*.[62]

Table 6 McMurry coupling reaction of carbonyl substrate containing sulfide and thiophene group

Substrate	Product	Source of metal	Reducing agent	Solvent	Yield	Ref.
38	**39**	$TiCl_4$	Zn	THF	84%	47
40a	**42a**	$TiCl_4$	Zn	THF	89%	48
40b	**42b**	$TiCl_4$	Zn	THF	48%	48
41	**43**	$TiCl_4$	Zn	THF	84%	48
44	**45**	$TiCl_4$	Zn	THF	83%	49

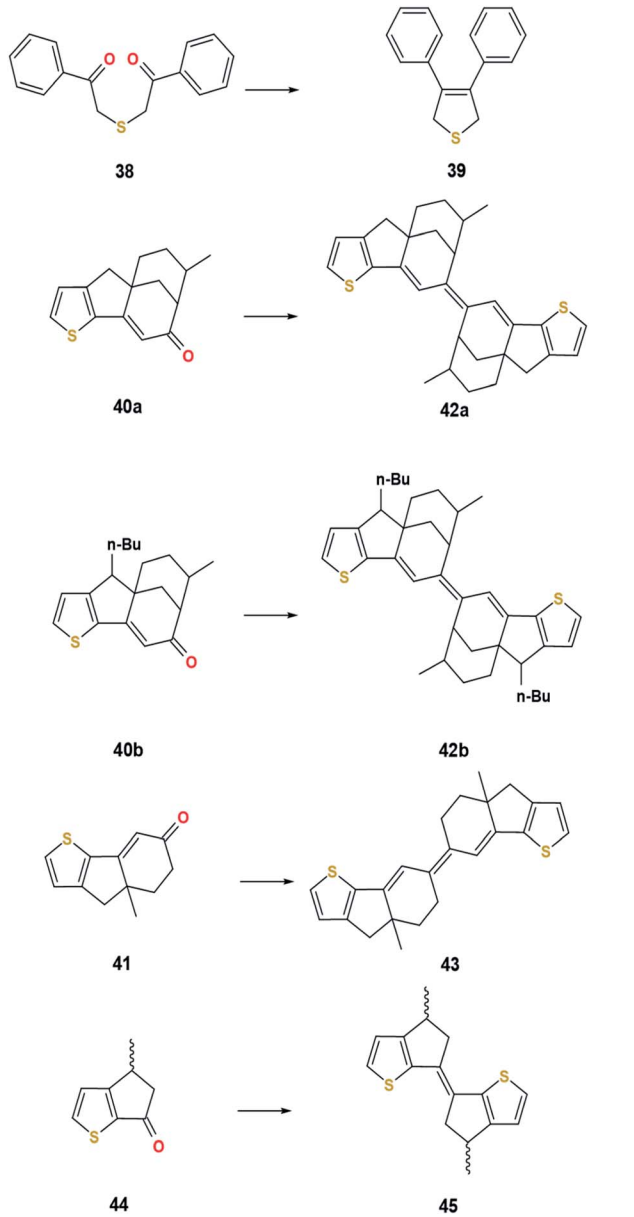

Fig. 12 McMurry coupling reaction of carbonyl substrate containing sulfide and thiophene groups.

4.2.2 Carboxylic acid. There is little information regarding experiments testing the resistance of carboxylic acid groups to the McMurry reaction conditions (Table 10). In 1981, Geise *et al.*

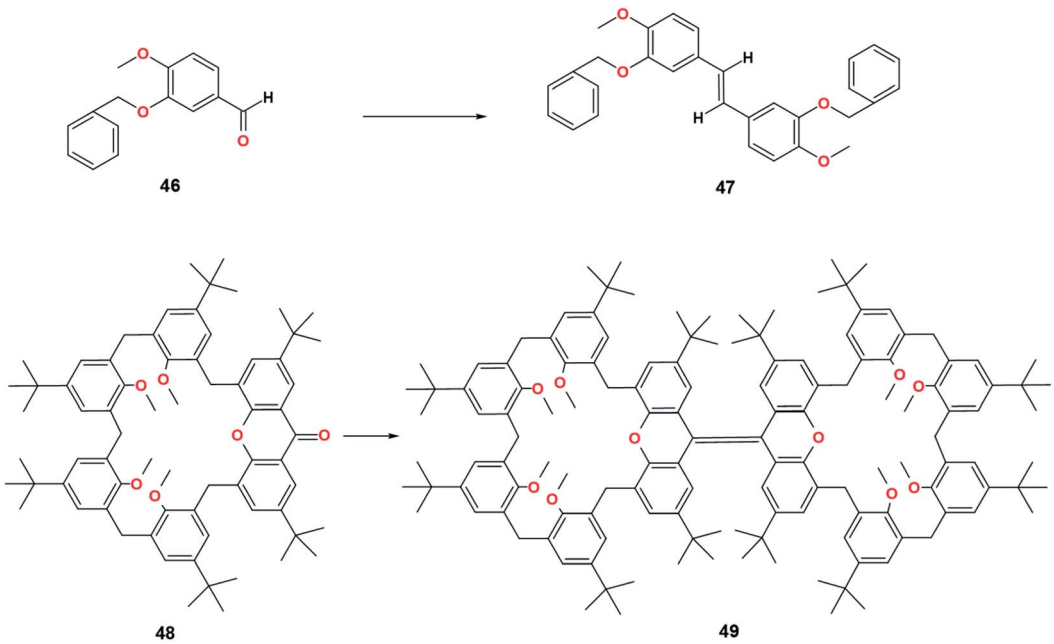

Fig. 13 McMurry coupling reaction of carbonyl substrate containing ether groups.

Table 7 McMurry coupling reaction of carbonyl substrate containing ether groups

Substrate	Product	Source of metal	Reducing agent	Solvent	Yield (%)	Ref.
46	**47**	$TiCl_3$	Zn–Cu	DME	97	50
48	**49**	$TiCl_4$	$LiAlH_4$	THF	18	51

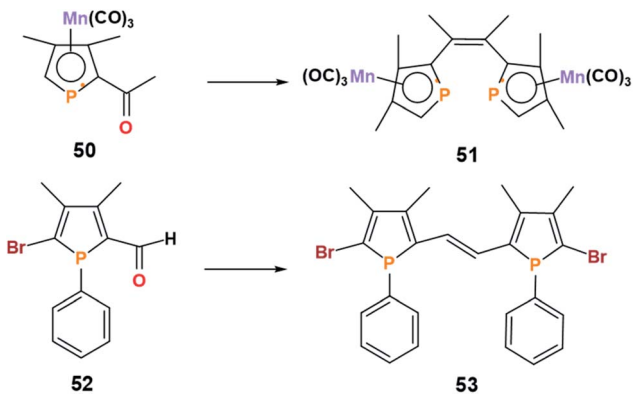

Fig. 14 McMurry coupling reaction of carbonyl substrate containing phospholes groups.

reported that the coupling reaction of benzoic acid, **76**, resulted in an assortment of products with different functional groups, **77–80** (Fig. 16).[63] One or both oxygen atoms from carboxylic acid or its salts can be abstracted by low-valent titanium to yields either alkyne or diketone. Partial reduction of alkyne using hydrogen gas with a Lindlar catalyst *via syn* addition mechanism or sodium with ammonia *via* anti-addition will produce olefins. According to McMurry's hypothesis, the transformation of the carboxylic acid group can be prevented by carrying the reaction in a relatively swift period.[13] Another way to prevent the reduction of the carboxylic acid group is by transforming the carboxylic acid groups into a specific group listed in Table 11. Inactivation of carboxylic acid groups by converting them to esters is less desirable because esters react slowly with low-valent titanium. Further research is needed to ensure that the protected carboxylic acid is compatible with the McMurry reaction.

4.2.3 Ester. In contrast to carboxylic acids, many coupling reactions of carbonyl compounds containing ester groups have been reported (Fig. 17). One example that describes the stability of an ester group against the McMurry reaction is the synthesis of olefin, **82**, from an ester substrate, **81**, *via* intramolecular coupling reaction.[64] The ester did not undergo a functional group transformation due to the presence of two carbonyls that close to each other. Hence, the intramolecular reaction between the two adjacent carbonyls is preferred rather than carbonyl from the ester. The synthesis of the lasiodiplodine-forming material describes some experiments showing the incompatibility of ester groups with the McMurry reaction, **84**,[65] and enol ether, **87**,[66] *via* intermolecular keto-ester couplings (Table 12).

Table 8 McMurry coupling reaction of carbonyl substrate containing phospholes group

Substrate	Product	Source of metal	Reducing agent	Solvent	Yield (%)	Ref.
50	**51**	$TiCl_4$	Zn	THF	27 (*meso*) 45 (*rac*)	52
52	**53**	$TiCl_4$	Zn	THF	68	53

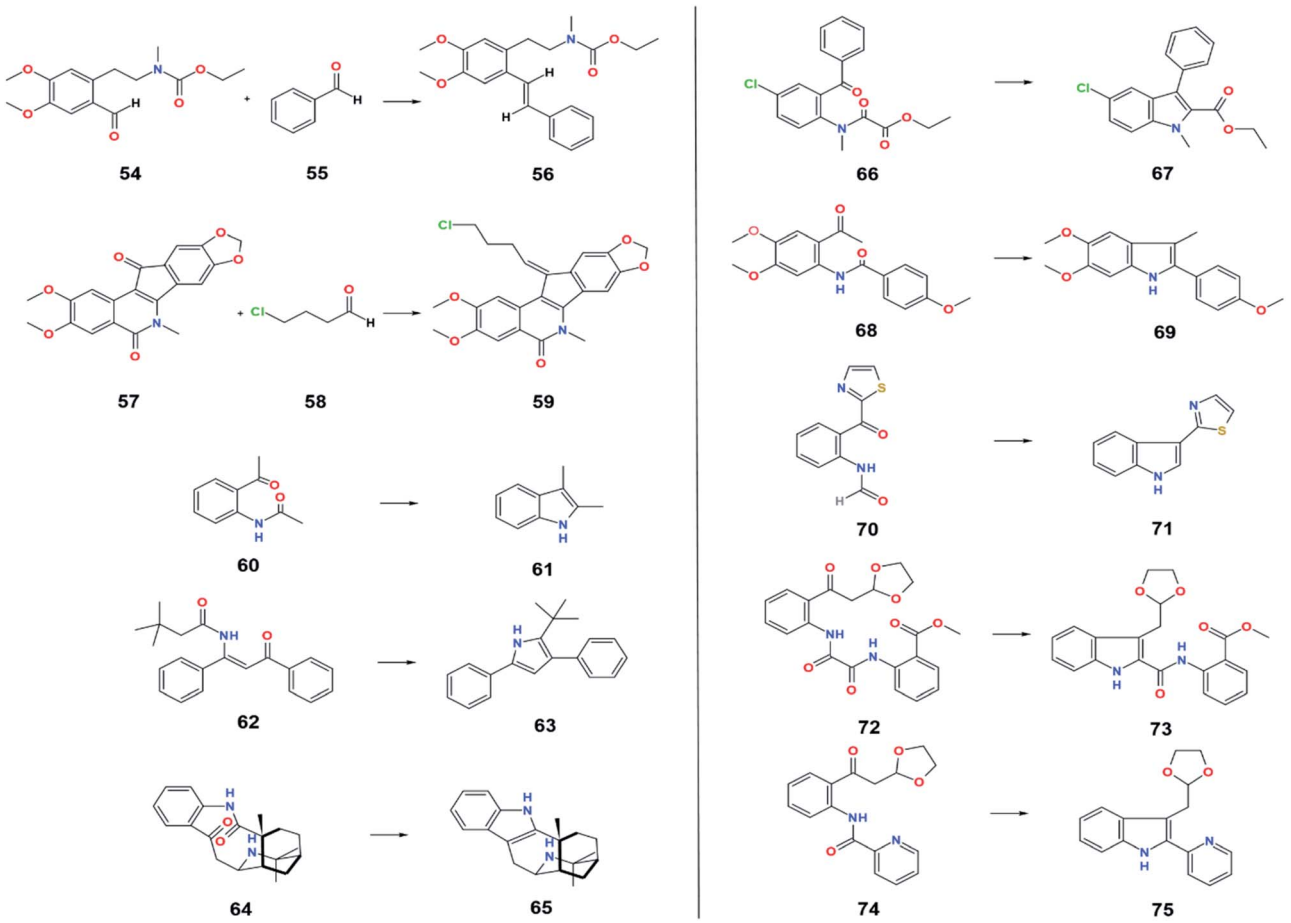

Fig. 15 McMurry coupling reaction of carbonyl substrate containing amide and oxoamide groups.

Table 9 McMurry coupling reaction of carbonyl substrate containing amide and oxoamide group

Substrate	Product	Source of metal	Reducing agent	Solvent	Yield (%)	Ref.
54 & **55**	**56**	$TiCl_3$	Li	1,2-DME	55	54
57 & **58**	**59**	$TiCl_4(THF)_2$	Zn	THF	43	55
60	**61**	$TiCl_3$	Graphite	THF	70	56
62	**63**	$TiCl_3$	Zn	DME	60	57
64	**65**	$TiCl_3$	Zn	THF	75	58
66	**67**	LVT	Graphite	DME	94	59
68	**69**	$TiCl_3$	C_8K	DME	66	60
70	**71**	$TiCl_3$	Zn	DME	71	61
72	**73**	$TiCl_3$	C_8K	THF	—	62
74	**75**	$TiCl_3$	C_8K	THF	57	62

4.2.4 Toluenesulfonate ester. In the field of organic synthesis, toluenesulfonate or tosylate groups are generally used as a protecting group. Although this group is compatible with the McMurry reaction, the existence of a strong nucleophile substituted the group resulting in an undesired product. This group is a good leaving group due to the resonance or electron delocalization of the negative charge on oxygen. One example that demonstrates the compatibility of the tosylate group is the synthesis of the compound, **89**, through the intermolecular coupling reaction of difunctional substrates, **88**.[50] By using $TiCl_3$/Zn–Cu system in THF, the product was successfully synthesized with 64% yield. Neither transformation nor substitution occurs during the McMurry reaction (Fig. 18).

4.2.5 Nitrile. The nitrile group can be compatible with the McMurry reaction as long as the reaction conditions and the reagent are selected correctly. This group is inert to low-valent titanium but can be reduced rapidly to primary amines in the presence of $LiAlH_4$ with diethyl ether solvent. The reaction's

Table 10 McMurry coupling reaction of carbonyl substrate containing carboxylic acid group

Substrate	Product	Source of metal	Reducing agent	Solvent	Yield (%)	Ref.
76	**77**	$TiCl_3$	$LiAlH_4$	THF	39	63
76	**78**	$TiCl_3$	$LiAlH_4$	THF	17	63
76	**79**	$TiCl_3$	$LiAlH_4$	THF	12	63
76	**80**	$TiCl_3$	$LiAlH_4$	THF	5	63

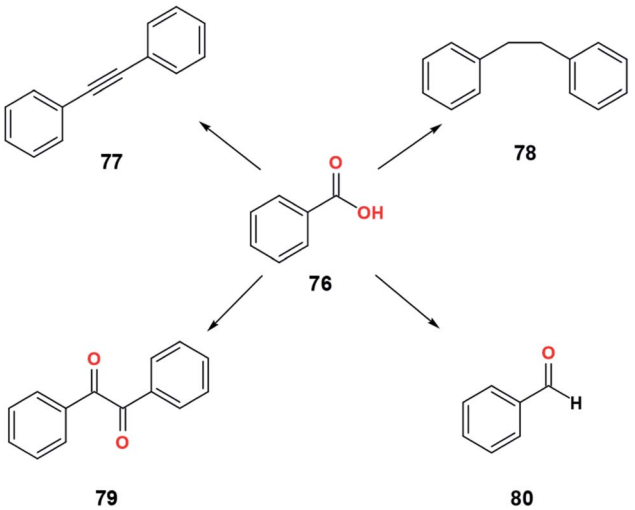

Fig. 16 McMurry coupling reaction of carbonyl substrate containing carboxylic acid groups.

atmosphere should be neither too acidic nor too alkaline because nitriles can be hydrolyzed to carboxylic acids or carboxylic salts in an acid or alkaline atmosphere. Adjusting the pH by adding acid or base reagents in the McMurry reaction is not recommended. In general, adding an acid reagent such as HCl can quench the reaction, whereas an excess base reagent can react with the titanium to form titanium hydroxide deposits. One experiment which shows the inert nature of the nitrile group against low-valent titanium ($TiCl_3/LiAlH_4$ system) is the formation of the nitrile compound, **91**, as minor products (yield = 15%) that did not undergo a further transformation (Fig. 19).[63] In 2018, Mai *et al.* succeeded in combining a nitrile group substrate to form an unsymmetrical *E*-alkenes *via*

Table 11 Protection and deprotection of carboxylic acid group

Transformation (deactivation state)	Deprotection (reactivation)
Methyl ester	Acid or base
Benzyl ester	Hydrogenolysis
Silyl ester	Organometallics, acid, and base
tert-Butyl ester	Reductants, acid, and base
Oxazoline	Strong acid or alkali[a]

[a] High temperature required.

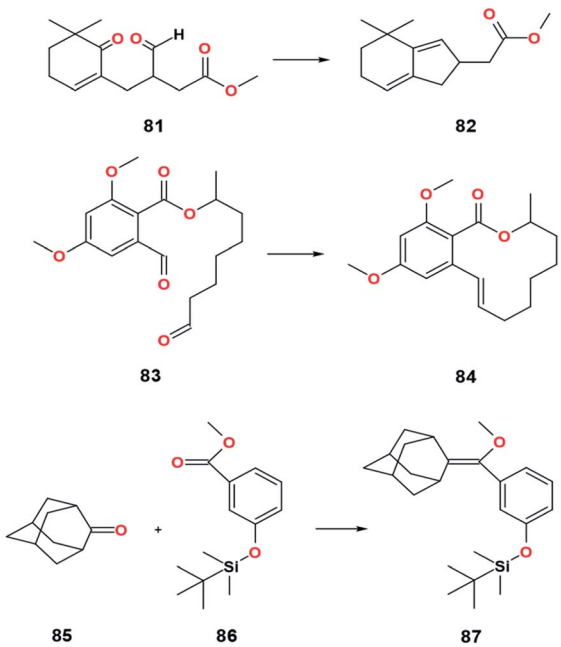

Fig. 17 McMurry coupling reaction of carbonyl substrate containing ester groups.

Table 12 McMurry coupling reaction of carbonyl substrate containing ester group

Substrate	Product	Source of metal	Reducing agent	Solvent	Yield (%)	Ref.
81	**82**	$TiCl_3$	Zn–Cu	DME	52	64
83	**84**	Ti	Graphite	DME	69	65
85 & **86**	**87**	$TiCl_3$	$LiAlH_4$	THF	41 up to 59	66

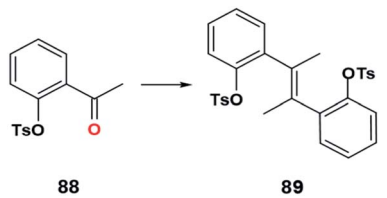

Fig. 18 McMurry coupling reation of carbonyl substrate containing tosylate groups.

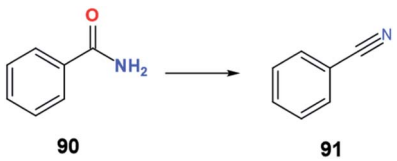

Fig. 19 McMurry coupling reaction of carbonyl substrate resulting nitrile compound as a minor product.

Table 13 Products obtained from the reaction of allylic alcohol and 1,2-diol compounds with low-valent titanium

Substrate	Product	Source of metal	Reducing agent	Solvent	Yield (%)	Ref.
92	**93**	$TiCl_3$	K	DME	85	7
94	**95**	$TiCl_3$	K	DME	80	7
96	**97**	$TiCl_3$	$LiAlH_4$	THF	87	69

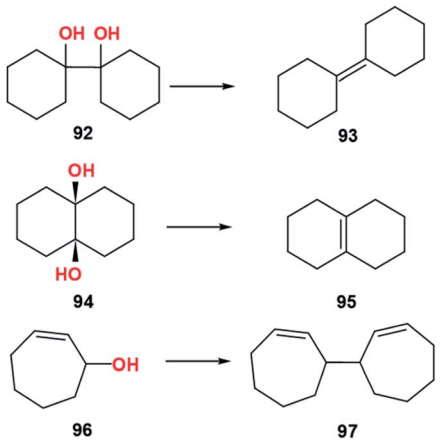

Fig. 20 Products obtained from the reaction of allylic alcohol and 1,2-diol compounds with low-valent titanium.

phosphaalkene and phosphine intermediates as an alternative to the olefination of carbonyl other than the McMurry reaction.[67]

4.3 Incompatible functional groups

Incompatible functional groups undergo a direct transformation when reacting with low-valent titanium. It is advisable to use other milder reactions than the McMurry reactions when involving a substrate containing this group. Some examples of non-compatible functional groups other than those described below include halohydrin, enedione, and quinone groups.

Table 14 Products obtained from the reaction of nitro compounds with low-valent titanium

Substrate	Product	Source of metal	Reducing agent	Solvent	Yield (%)	Ref.
98	**99**	$TiCl_3$	$LiAlH_4$	THF	63	63
98	**100**	$TiCl_3$	$LiAlH_4$	THF	23	63
98	**101**	$TiCl_3$	$LiAlH_4$	THF	5	63
102 & **103**	**104**	$TiCl_4$	Zn	THF	74	70
105 & **106**	**107**	$TiCl_4$	Sm	THF	74	71
108	**109**	$TiCl_3$	—	THF	62	72

4.3.1 Alcohol (allylic alcohol and 1,2-diol). As discussed in the section on the reaction mechanism, hydrolysis of metallopinacolate as an intermediate in the first step of the McMurry reaction yields 1,2-diol compounds. The presence of two adjacent oxygen atoms can be easily abstracted by active titanium, resulting in carbon radicals on the substrate that can interact with the adjacent carbon radicals to form new carbon–carbon bonds. For example, 1,2-diol, **92** and **94**, can be deoxygenated to form a new carbon–carbon bond, **93** and **95**.[7] The addition of 2-dimethoxypropane, boc-ethylidene, moc-ethylidene, and other diol protection agents should prevent the deoxygenation process.[68] Further investigation of these protecting agents are needed to test the effect on the synthesized product. Besides 1,2-diol, allylic alcohol is also a group that can be reduced by active titanium. For example, dienes compound, **97**, can be obtained from the intermolecular coupling of 2-cyclohepten-1-ol, **96** (Table 13).[69] All of the reactions have been illustrated in Fig. 20.

4.3.2 Nitro. The reduction of the nitro group is one of the reactions to obtain a wide variety of functional groups. Several experiments related to the reaction of nitro groups with low-

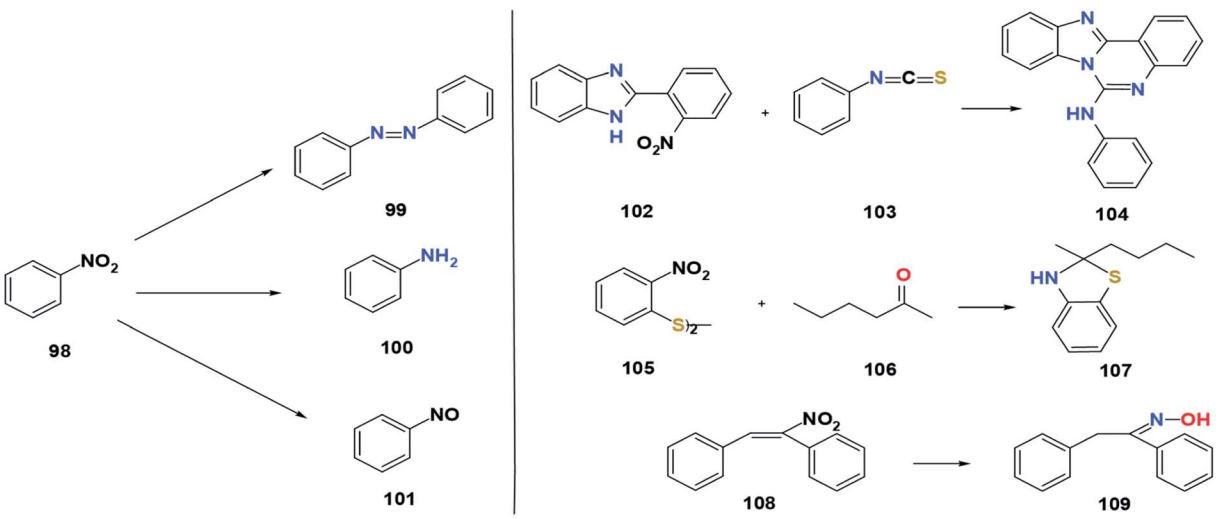

Fig. 21 Products obtained from the reaction of nitro compounds with low-valent titanium.

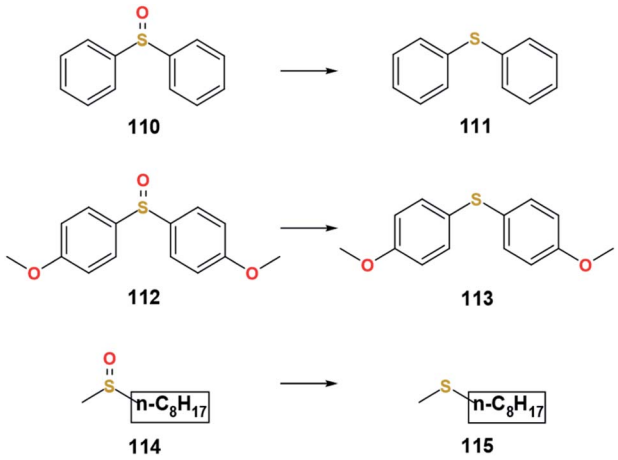

Fig. 22 Products obtained from the reaction of sulfoxide compounds with low-valent titanium.

Table 15 Products obtained from the reaction of sulfoxide compounds with low-valent titanium

Substrate	Product	Source of metal	Reducing agent	Solvent	Yield (%)	Ref.
110	**111**	$TiCl_3$	—	MeOH & $CHCl_3$	63	73
112	**113**	Cp_2TiCl_2	In	THF	92	74
112	**113**	$TiCl_4$	In	THF	95	75
114	**115**	TiI_4	—	CH_3CN	90	76

Table 16 Products obtained from the reaction of epoxide compounds with low-valent titanium

Substrate	Product	Source of metal	Reducing agent	Solvent	Yield (%)	Ref.
116	**117**	$TiCl_3$	$LiAlH_4$	THF	53	77
118	**119**	Cp_2TiCl_2	Mn	H_2O	92	78
120	**121**	Cp_2TiCl_2	Mn	H_2O	95	78
122	**123** & **124**	Cp_2TiCl_2	Zn	THF	68 (1 : 3.5)	79

valent titanium have shown the transformation from nitro group to azo, aniline, nitroso, amine, oxime, and amino groups (Fig. 21).[63,70–72] The presence of 2 phenyl groups on the substrate, **108**, stabilizes the radical anion obtained from the electron transfer of titanium(III) to the nitro group. Reduction of these radical anions produced an oxime, **109**, which can be further reduced to form imine by aqueous titanium halide.[65] The ability of oxime to be reduced by low valence titanium shows the incompatibility of this group in the McMurry reaction (Table 14).

4.3.3 Sulfoxide. Reduction of sulfoxide using $LiAlH_4$, $NaBH_4$–$FeCl_3$, low valent titanium, or other reducing agents yields a sulfide group. Some experiments related to the transformation of sulfoxides to sulfides have been illustrated in Fig. 22. Coordination of titanium halide with oxygen attacks one

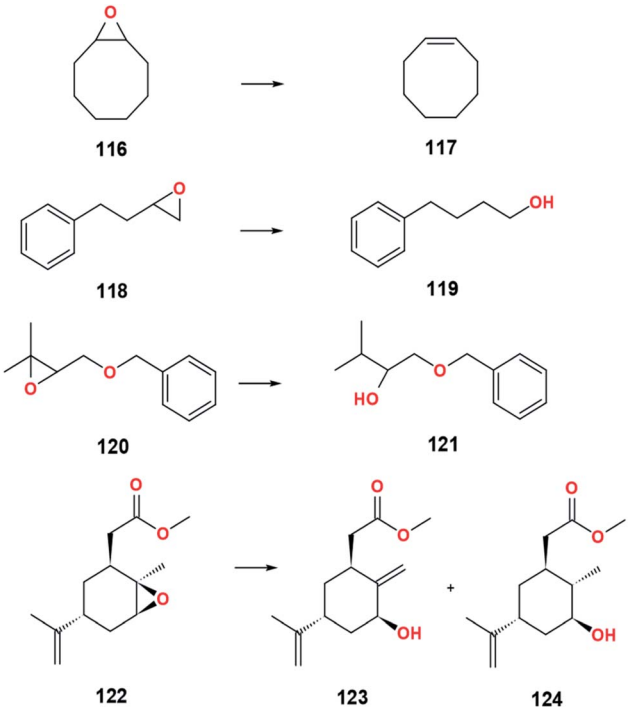

Fig. 23 Products obtained from the reaction of epoxide compounds with low-valent titanium.

of the halide ligands to give the intermediate halogenated species. The other halide anion attacks the intermediate species resulting in a deoxygenated sulfide (Table 15).[73–76]

4.3.4 Epoxide. The reaction of the epoxide with low-valent titanium produced an alcohol compound that can be further reduced to give olefins. Single-electron transfer from low-valent titanium could generate a regioselective radical epoxide opening. The epoxide opening mechanism involves the most substituted radical that is energetically stable in an acidic atmosphere or the less substituted radical in an alkaline atmosphere. Some of the reactions showing the transformation of epoxide groups into alcohols and alkenes are listed in Table 16 have been illustrated in Fig. 23.[77–79]

Table 17 McMurry reaction of β-ionone[a][80]

Coupling reagent	Additive	Temperature (°C)	Reaction time (h)	Yield (%)		
				126	**127**	**128**
A	—	−10 °C	1	—	94	—
B	—	Reflux	1	44	8	25
B	*n*-Bu_3N	Reflux	3	70	—	20
B	*n*-Bu_3N	Reflux	3	91	—	—
A	*n*-Bu_3N	Reflux	3	63	20	—
B	Pyridine	Reflux	3	82	—	—
B	$(C_2H_5)_3N$	Reflux	3	82	—	—
B	PS	Reflux	3	94	—	—
B	DABCO	Reflux	3	72	—	—

[a] A = $TiCl_4$/Zn; B = $TiCl_4$/$LiAlH_4$; PS = proton sponge.

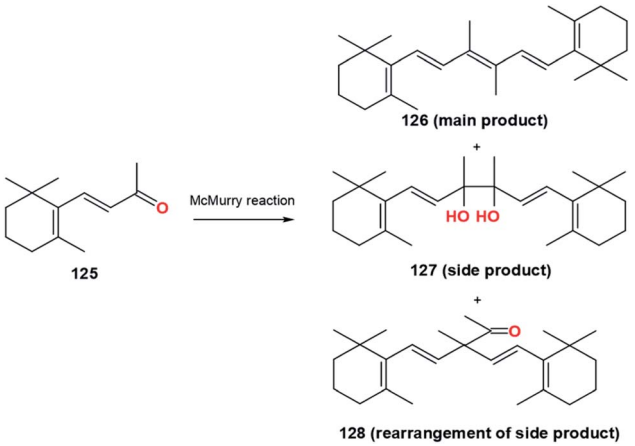

Fig. 24 McMurry reaction of β-ionone.[80]

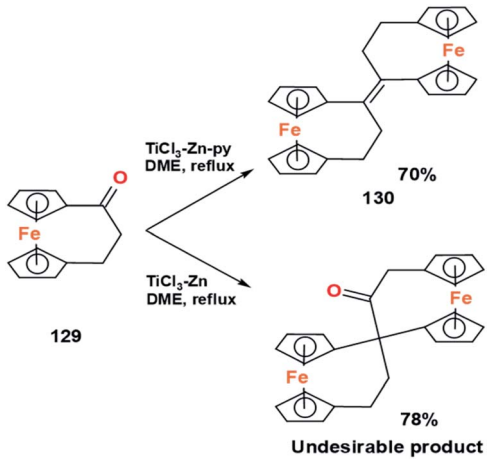

Fig. 25 McMurry coupling of a ferrocenyl ketone with (top) and without (bottom) the presence of pyridin.[81]

5. Effects of additives

The regulation of low-valent titanium activity has been reached by adding an additive compound or changing the reaction conditions. In some instances, additives improve the reactivity of $TiCl_x$-reducing agent systems resulting in an enhancement of olefin's formation at high-temperature reactions or, on the contrary, a pinacol at low to room-temperature reactions.

5.1 Addition of amine compounds

In 1976, Ishida and Mukaiyama conducted an experiment that showed the selectivity of olefin's formation after adding various amine compounds (Table 17).[80] Some of the tertiary amine reagents consist of tri-*n*-butylamine, pyridine, triethylamine, proton sponge (1,8-bis(dimethylamino)naphthalene), and DABCO (1,4-diazabicyclo[2.2.2]octane). The results show that the addition of tertiary amine reagents suppressed the formation of pinacol, **127**, and its rearrangement, **128**.[80] The presence of this additive serves to maintain the reaction atmosphere in an alkaline state to prevent protonation of metallopinacolate intermediates (Fig. 24).

Another experiment (Fig. 25) shows the role of pyridine to prevent the formation of the pinacol rearrangement product, namely synthesis of *E.Z*-bis([3]-ferrocenophane-1-ylidene), **130**, from the coupling of [3]-ferrocenophan-1-one, **129**.[81] It shows that the presence of pyridine can increase the selectivity of the McMurry reaction in producing olefins.

5.2 Addition of alkali metal salts, alkaline earth metal salts, arene, bromide and iodine

Several trials to observe the additive effect of alkali metal salts, alkaline earth metal salts, bromide, iodine, and arene have been reported (Table 18).[82–84] Some of these additives increased the activity and *E*-selectivity of the $TiCl_x$–Li system. The experiment used acetophenone, **131**, as substrate in $TiCl_3$–Li system coupled to form stilbene, **132**, with a minor product in the form

Table 18 McMurry reaction of acetophenone with various additives

Additives	Temperature (°C)	Reaction time (h)	Yield (%)		Ref.
			132 (*E* : *Z*)	**133** (*dl* : *meso*)	
—	Reflux	16	89 (75 : 25)	—	82
—	0–5	16	Trace	87 (75 : 25)	82
I_2	0–5	2	90 (80 : 20)	—	82
Ethyl bromide	0–5	5	25	67 (80 : 20)	82
1,2-Dibromoethane	0–5	5	87	—	82
LiI	25	16	Trace	75 (80 : 20)	83
KCl	25	2	82 (85 : 15)	—	83
CsCl	25	2	65 (70 : 30)	—	83
$MgCl_2$	25	16	25 (65 : 35)	62 (70 : 30)	83
Anthracene	25	3	70 (70 : 30)	Trace	84
Naphthalene	Reflux	1.5	89 (56 : 44)	—	84
Naphthalene	25	2	77 (68 : 32)	Trace	84
Naphthalene	25	6	68 (30 : 70)	18 (75 : 25)	84

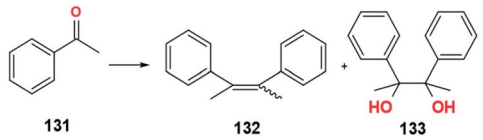

Fig. 26 McMurry reaction of acetophenone.[82]

Table 19 Effect of Lewis acid on the radical reaction of functionalized alkenes with substituted vinylcyclopropanes (Reaction 1) and radical reduction of methyl (±)-2-(1-methoxy-1-phenylmethyl)propenoate (Reaction 2)

Reaction	Lewis acid	Temperature (°C)	Product Ratio (*E* : *Z*)	Yield (%)	Ref.
1	—	Reflux	4.4 (**136**) 1.9 (**137**) 1.2 (**138**) 1.0 (**139**) 10.6 (**136**)	53	85
1	$AlMe_3$	−50	4.1 (**137**) 1.4 (**138**) 1.0 (**139**)	52	85
2	—	0	1.0 (**141**) 4.0 (**142**)	49	86
2	$MgBr_2 \cdot OEt_2$	0	6.0 (**141**) 1.0 (**142**)	49	86

of 1,2-diol compounds, **133**.[82] One of the advantages of using naphthalene and I_2 additives is the high formation of olefin product in the low-temperature reaction. Moreover, the McMurry reaction in the $TiCl_3$–Li–naphthalene system has a faster reaction time than the typical McMurry reaction. Additional information from the experiment shows that the main product is dominant in the *E* configuration compared to the *Z* configuration. Energetically, the *Z* configuration is more unstable than the *E* configuration because the two adjacent larger groups collide, forming an electrical repulsion that destabilizes the molecule (Fig. 26).

6. Effects of Lewis acid, electron withdrawing group, and electron donating group

The first step of the McMurry reaction involves a single electron transfer from the active titanium to the carbonyl group. The carbonyl group needs to be activated to increase its ability to attract electrons from the titanium. Generally, activation of the carbonyl group can be performed by adding Lewis acid. Lewis acid can accept electrons from the carbonyl causing the group to become positively charged. It creates an electron-poor carbonyl with more tendency to attract electrons stronger than an inactivated carbonyl. Apart from carbonyl activation, some experiments have shown that Lewis acid increases radical reactions' selectivity (Table 19, Fig. 27).[85,86] In the McMurry reaction, the TiX_n compound also acts as Lewis acid. The Lewis acidity of TiX_n is altered from mild to strong by replacing X from alkoxide to halide to triflate group.

Aside from adding Lewis acid, activation of the carbonyl group can also be carried out by utilizing an electron-attracting functional group or commonly known as the electron-withdrawing group (EWG group). The EWG can draw electrons from adjacent carbonyl towards themselves by resonance

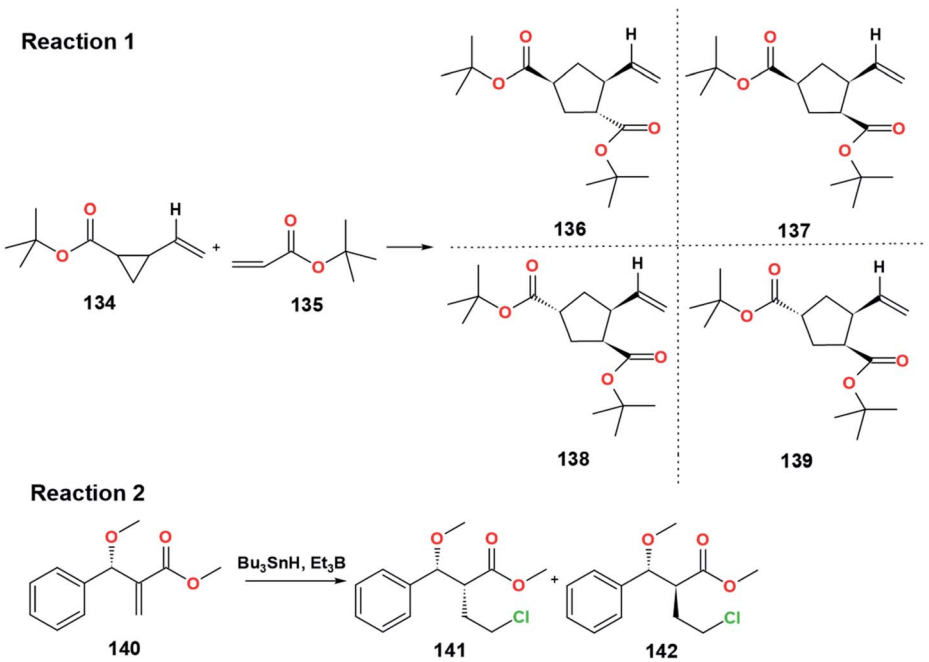

Fig. 27 Effect of Lewis acid on the radical reaction of functionalized alkenes with substituted vinylcyclopropanes (Reaction 1) and radical reduction of methyl (±)-2-(1-methoxy-1-phenylmethyl)propenoate (Reaction 2).[85,86]

Table 20 List of electron donating group (EDG) and electron withdrawing group (EWG)[a]

Substituent	Classification	Electronic effect		Magnitude
		I	M	
Oxido	EDG	+	+	Very strong
Hydroxy and ether		−	+	Strong
Amino		−	+	Strong
Acyloxy		−	+	Moderate
Acylamido		−	+	Moderate
Alkylthio and sulfhydryl			+	Moderate
(Di)alkylphosphino			+	Moderate
Phenyl		−	+	Weak
Vinyl		−	+	Weak
Alkyl		+		Weak
Anion carboxylate		+		Weak
Fluoro (*para* position)		−	+	Weak
Nitro	EWG	−	−	Strong
Sulfonic acid and sulfonyl		−	−	Strong
Trifluoromethylsulfonyl		−	−	Strong
Trisubstituted ammonium		−		Strong
Cyano		−	−	Strong
Trihalomethyl		−		Strong
Acyl halide, aldehyde, ketone		−	−	Moderate
Carboxylic acid and ester		−	−	Moderate
Amide		−	−	Moderate
Nitroso		−	±	Weak
Halide		−	+	Weak
Fluoro (*ortho* and *meta* position)		−	+	Weak

[a] +I (inductively electron donor), −I (inductively withdrawing electron), +M (electron donor *via* resonance), −M (withdrawing electron *via* resonance).

or inductive effects, causing an electron deficiency in the carbonyl group. In contrast to EWG, the presence of EDG reduces the reactivity of the carbonyl. An electron-donating group (EDG) donates some of its electrons into a conjugated π system such as carbonyl by resonance or inductive effects, causing the carbonyl tends to be difficult to accept electrons from titanium. By understanding the concepts of EWG and EDG, it can be hypothesized that the presence of EWG adjacent to carbonyl could increase the amount of olefin.

On the other hand, EDG could decrease the amount of olefin. Apart from analyzing the existence of EWG and EDG, determining each group's type of electronic effect is also very important. Although the EDG could deactivate carbonyl, some EDGs can attract electrons from the carbonyl inductively. Thus, the functional group categorized as EDG but able to attract electrons inductively would slightly enhance the olefin yield compared to the inductive electron donor. Several groups classified as EWG and EDG are listed in Table 20.

In 1981, Castedo *et al.* tested the effects of EDG substituents on carbonyl coupling reaction using $TiCl_3$/Zn–Cu system

Table 21 Carbonyl olefination in $TiCl_3$/Zn–Cu system with various functional groups[50]

Substrate	Functional group				Product	Yield (%)
	R^1	R^2	R^3	R^4		
143a	CH_3O	AcO	H	H	**144a**	97
143b	CH_3O	$CH_3OOCCH_2CH_2OCO$	H	H	**144b**	60
143c	AcO	CH_3O	H	H	**144c**	87
143d	AcO	H	H	H	**144d**	94
143e	AcO	H	H	CH_3	**144e**	64

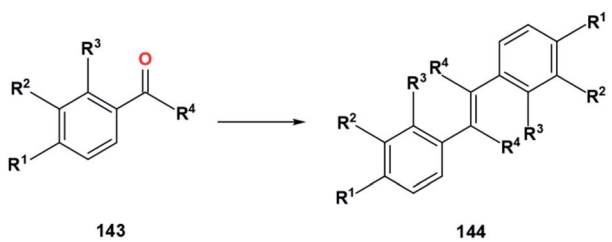

Fig. 28 Carbonyl olefination in $TiCl_3$/Zn–Cu system with various functional groups.[50]

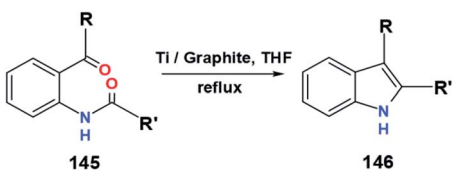

Fig. 29 Synthesis of indole derivatives with various functional groups through McMurry coupling reaction.[56]

Table 22 Synthesis of indole derivatives with various functional groups through McMurry coupling reaction[56]

Substrate	Functional group R	Functional group R′	Reaction time (h)	Product	Yield (%)
145a	Me	Ph	8	**146a**	75
145b	Me	Me	8	**146b**	70
145c	Ph	Ph	8	**146c**	90
145d	Ph	Me	8	**146d**	87
145e	Ph	H	8	**146e**	92

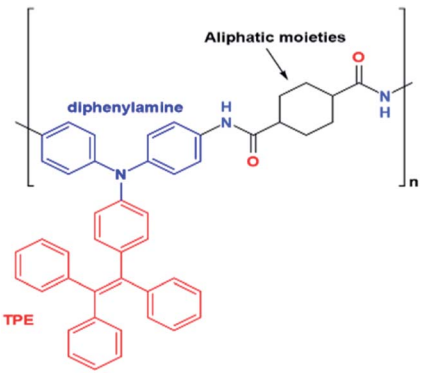

Fig. 30 Design strategy of a modified TPE-based electrofluorochromic material.[93]

(Fig. 28).[50] In this section, it is shown that the effects of substituents at the *para* (R_1) and *ortho* (R_3) positions relative to the carbonyl group are more significant compared to meta position. Therefore, R^2 can be neglected as long as the R^2 group is not bulky (steric effect). The steric effect is shown here when comparing **143a** and **143b**. By substituting acyloxy (AcO), **143a**, at R^2 with the bulky $CH_3OOCCH_2CH_2OCO$ (**143b**), the yield drops from 97% to 60%.

In term of electronic effect, the direct exchange of the R^1 and R^2 group between methoxy, **143a**, and acyloxy (AcO), **143c**, decreases the yield from 97% to 87%. Methoxy is a stronger EDG compared to acyloxy. As previously discussed, the presence of EDG will donate electrons to the aromatic ring. The electrons contained in the aromatic ring will be attracted by the carbonyl, causing the oxygen contained in the carbonyl to be more electron-rich and easier to bond with titanium. This might be the cause of the yield decrease.

However, the steric effect also plays a role in here since when there is no methoxy, **143d**, the yield increases to 94%. Another example of the significance of steric effect is on **143e**. The presence methyl at R^4, even though known as EDG, gives a lower yield at 64% (Table 21).

McMurry coupling of a substrate with various functional groups to produce indole derivatives by Fürstner and Jumbam (Fig. 29) also showed the expected result.[56] Based on the data in Table 22, the replacement of the R group gives a significant difference in results compared to the R′ group. The presence of an amino group adjacent to the carbonyl is predicted to affect the induction from R′, especially amino groups able to attract electrons inductively. Since methyl inductively donating electrons while phenyl inductively withdrawing electrons, exchanging the functional group from phenyl to methyl reduced the amount of indole, **146**, synthesized.[56] However, even though the reaction is an intramolecular reaction between two adjacent carbonyls, the steric factor also needs to be considered.

There are still many factors to increase or decrease the yield of synthesized products, such as steric effects, types of interaction, reaction conditions, reagents, and others. Some of the previously described experiments have slightly different reaction conditions. Therefore, further research is needed to determine the effect of EWG and EDG on carbonyl reactivity without being affected by other factors.

7. Applications of the McMurry reaction

7.1 Synthesis of non-natural products

Numerous synthetic applications of the McMurry coupling reaction in preparing crowded, strained, and polyaromatic alkenes have been reported (Fig. 31). Non-natural products are materials or compounds that can only be obtained through synthesis and cannot be produced by living organisms. In the field of organic electronics, the McMurry reaction is used to prepare a double-helical compound, **148**, as a precursor to synthesize naphthotetraindole cores.[15] Further treatment of **148** with Cu(I) salt and AgOAc as an oxidant with the addition of PivOH could produce naphthotetraindole with a yield of 67%.[15] The use of the conventional McMurry method utilizing the $TiCl_4$–Zn–THF system could produce a moderate yield due to four aromatics stabilizing the substrate, **147**. Naphthotetraindole is one of the polycyclic aromatic hydrocarbons (PAHs) as promising organic-based electronics. Generally, compounds belonging to the PAHs group can be obtained from coal and oil deposits. However, naphthotetraindole can only be acquired through organic synthesis pathways that also utilize several inorganic compounds. The presence of a large electron conjugation system in PAHs makes it a candidate for high-performance optoelectronic devices, such as organic-based LEDs, solar cells, and transistors.[15] The properties of each compound belonging to PAHs are relatively different due to the various magnitude of the electron conjugation system in PAHs. However, in general terms, PAHs are uncharged and non-polar molecules. One of the other intriguing things about PAHs is the variation of the redox potential that depends on the size of the PAHs. Radical formation of PAHs may be formed when present in McMurry system. Radical PAHs could interact with the same or different radical PAHs, creating larger conjugated systems with new physicochemical and chemical properties.[87]

In 2018, the group of Nakamura succeeded in synthesizing tetrakis(benzo[*b*]furyl)ethene (TBFE), **150**. This compound is known as an aggregation-responsive dye for their fluorescence-switching property.[30] TBFE adopts three switching stages involving intramolecular charge transfer and aggregation-

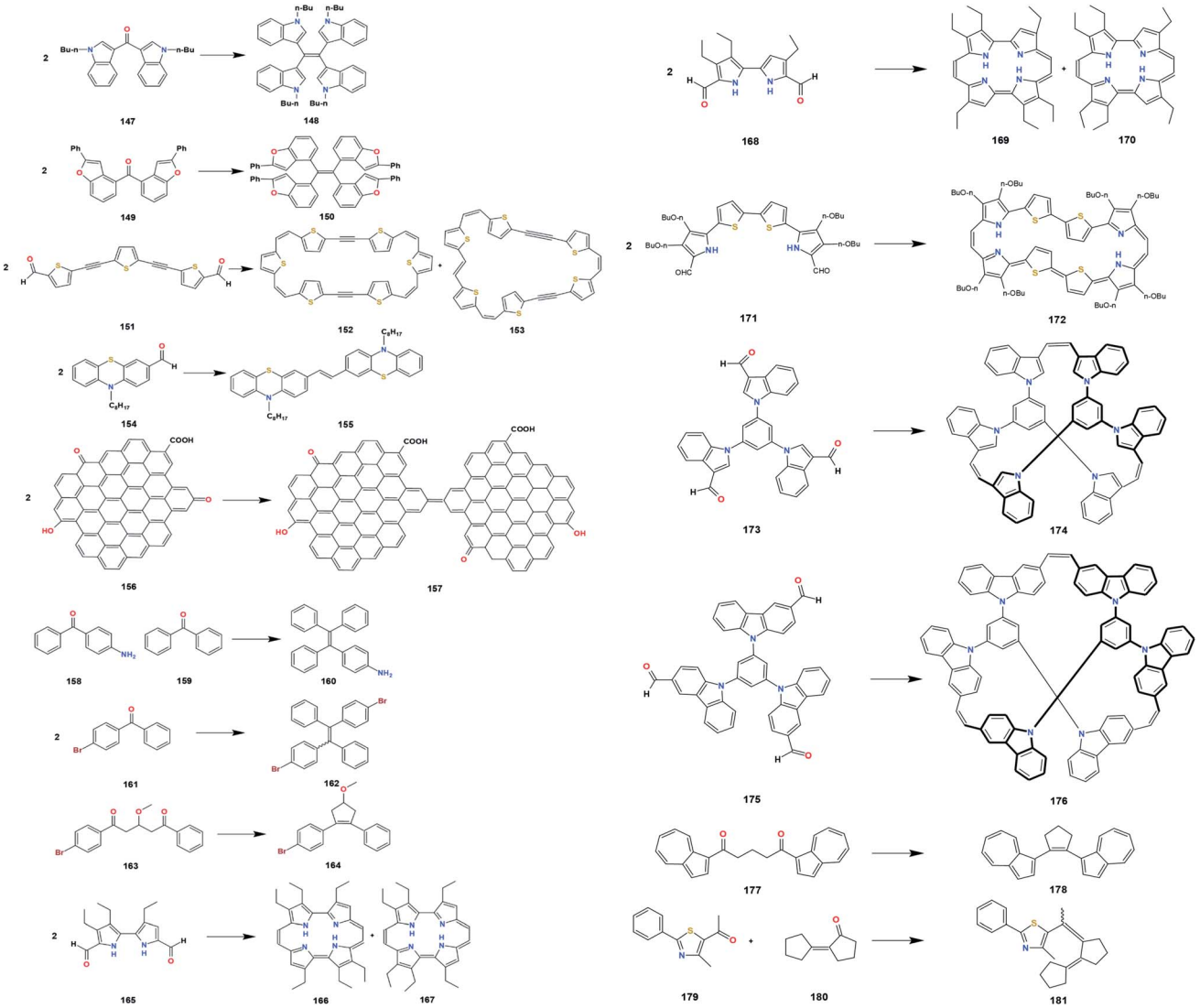

Fig. 31 Application of McMurry reaction in synthesis of non-natural products.

induced emission. According to Hamada, the change in TBFE's wavelength occurred by changing the composition of the solvent. The presence of solvents such as water affected the size of TBFE due to the polarity difference between TBFE and water. In this experiment, the low-valent titanium was replaced by low-valent hafnium due to the involvement of sterically hindered compounds. The use of hafnium is easier to reduce the carbonyl than titanium because of its lower standard reduction potential than titanium ($E_{Hf^{4+}/Hf} = -1.55$ V, $E_{Ti^{4+}/Ti} = -1.37$ V). Another application of the McMurry reaction is related to the reduction of ethynylene-linkage substrates to form a photosensitive product with vinylene-linkage units, **152** and **153**.[88] Oligothiophenes with π-conjugated macrocycles exhibit optoelectronic properties for multifunctional materials. Based on Shirahata's experiment, the yield of oligothiophene depends on the reaction temperature, the amount of titanium, and the thiophene substituent.[88]

A new novel synthetic of oligomers is a combination of the McMurry reaction, the Wittig reaction, and the Heck reaction applied to synthesize vinylene-linked molecules, **155**, specifically phenothiazinevinylene-based oligomers.[89] Phenothiazine has a bent-shape conformation, known as "butterfly" geometry, that can induce molecular aggregation and excimer formation. An excimer is a short-lived complex formed between two identical molecules whose composition is a molecule in the excited and ground states. According to Cibotaru *et al.*, phenothiazine excimers can inhibit the quenching luminescence process.[90] This process is crucial in making organic-based LEDs because LEDs are expected to have a constant light intensity. The bent-shape structure of phenothiazine is a result from the two heteroatoms with electron-donor characters on the corner point of the ring. Phenothiazine can develop a supramolecular structure with the involvement of large intermolecular distances. The large intermolecular distance of phenothiazine

Table 23 Application of McMurry reaction in synthesis of non-natural products

		Reagent				Condition			
Substrate	Product	Source of metal	Reducing agent	Solvent	Additive	Reaction time (h)	Temperature (°C)	Yield (%)	Ref.
147	**148**	$TiCl_4$	Zn	THF	—	Over-night	Reflux	56	15
149	**150**	$HfCl_4$	Zn	CH_3CN	—	48	70	50	30
151	**152** & **153**	$TiCl_4$	Zn	THF	Pyridine	18	66	10 (**152**); 4 (**153**)	88
154	**155**	$TiCl_4$	Zn	THF	Pyridine	12	Reflux	63	89
156	**157**	$TiCl_4$	Zn	THF	—	24	66 (reflux)	—	91
158 & **159**	**160**	$TiCl_4$	Zn	THF	Pyridine	12	Reflux	61	93
161	**162**	$TiCl_4$	Zn	THF	Pyridine	12	Reflux	80	94
163	**164**	$TiCl_4$	Zn	Dioxane	—	3	Reflux	63	95
165	**166** & **167**	$TiCl_4$	Zn	THF	CuCl	2	Reflux	8	96
168	**169** & **170**	$TiCl_4$	Zn	THF	CuCl	2	Reflux	15	96
171	**172**	$TiCl_4$	Zn	THF	CuCl	16	Reflux	30	97
173	**174**	$TiCl_4$	Zn	THF	Pyridine	12	Reflux	16	98
175	**176**	$TiCl_4$	Zn	THF	Pyridine	12	Reflux	14	98
177	**178**	$TiCl_4$	Zn	THF	Pyridine	1	0	88	99
179 & **180**	**181**	$TiCl_4$	Zn	THF	Pyridine	1.75	Reflux	48 ($E:Z = 1:3$)	100

could facilitate the luminescence of the compound in the solid state. The ability of phenothiazine to delocalize electrons and maintain charge mobility might enhance optical and electronic properties. Phenothiazine was first used as an insecticide and as a drug to treat parasitic worm infections. In addition, phenothiazine can also be used as a sedative, antitumor, antiallergies, antimalarial, analgesic, antifilarial, trypanocidal, and antipyretics.[89,90] Other than that, phenothiazine derivative compounds also have high bioactive activity in dealing with allergies. One of the disadvantages of using phenothiazines is the difficulty of these compounds to dissolve in water, thus requiring polar solvents, which are generally harmful to the environment. In the latest 2020, PEGylated phenothiazine derivatives were successfully synthesized by Cibotaru *et al.*[90] PEGylated phenothiazine is a response to environmental problems caused by phenothiazines. Based on the experiment, the synthetic PEGylated phenothiazine derivative can be dissolved in water or organic solvents such as acetone, DMF, ethanol, methanol, and THF with concentrations below 100 mM.[90] *In vivo* PEGylated phenothiazine testing showed cytotoxicity against cervical cancer cells and biocompatibility on human dermal fibroblasts.[90]

Enhancing optical and electronic properties can also be achieved by utilizing Graphene Quantum Dots (GQD) material. In 2017, nano GQDs, **157**, was successfully crosslinked by Chen *et al. via* intermolecular McMurry reaction catalyzed by $TiCl_4$ and Zn dust in refluxing THF.[91] GQD is a material derived from both carbon dots (CD) and graphene. The formation of GQDs sheets through the McMurry reaction is of particular interest because, with relatively inexpensive reagents, it can form nanosized products that have the potential to become optoelectronic materials, catalysts, storage, and energy generation.[91] One of the advantages of GQDs materials is their use to manufacture and develop photoluminescence-based sensors with the observed colors generally blue and green. In the field of biomaterials, GQDs are used as biosensors to detect the presence of double-stranded DNA (ds-DNA) methylated by DNA methyltransferase I. This is important considering that the presence of abnormal enzyme expression can cause cancer.[92] Through this experiment also proved the advantages of the McMurry reaction method for coupling bulk and conjugated substrates.

McMurry coupling reaction is also used to synthesize tetraphenylethylene (TPE) derivatives, **160** and **162**, as a candidate for electrochromic (EC) and aggregation—induced emission (AIE)-polyamide materials.[93,94] The McMurry reaction produces olefins with a mixture of *E* and *Z* isomers which are difficult to separate. To respond to these problems, adding certain functional groups to TPE can cause polarity differences between the *E* and *Z* isomers. This difference in polarity causes the mixture of *E* and *Z* isomers to be separated easily by polarity-based separation instruments such as HPLC. EC materials exhibit color due to the presence of conjugated polymers that can absorb visible light. Furthermore, the color change in EC occurs reversibly through a redox reaction. Redox reactions can cause changes in the charges of the species that are present in the EC material. In some instances, the difference in charge on certain species causes a significant color change. For example, Fe^{2+} has a green color while Fe^{3+} has an orange-brown color. In 2018, sun designed a modified TPE-based electrofluorochromic material with diphenylamine containing aliphatic moieties at the para position against TPE (Fig. 30). The presence of diphenylamine serves as an electroactive site and acts as fluorochromes. Fluorochrome is a chemical compound that can re-emit light upon excitation by light. The aliphatic moieties prevent fluorescence quenching by decreasing the effect of charge transfer. The para position is suggested to ensure the electrochemical stability of the modified TPE.[93]

A simple and efficient asymmetric synthesis of diaromatic compounds as a precursor for phenanthrenes also utilized the intramolecular McMurry coupling reaction of a substrate

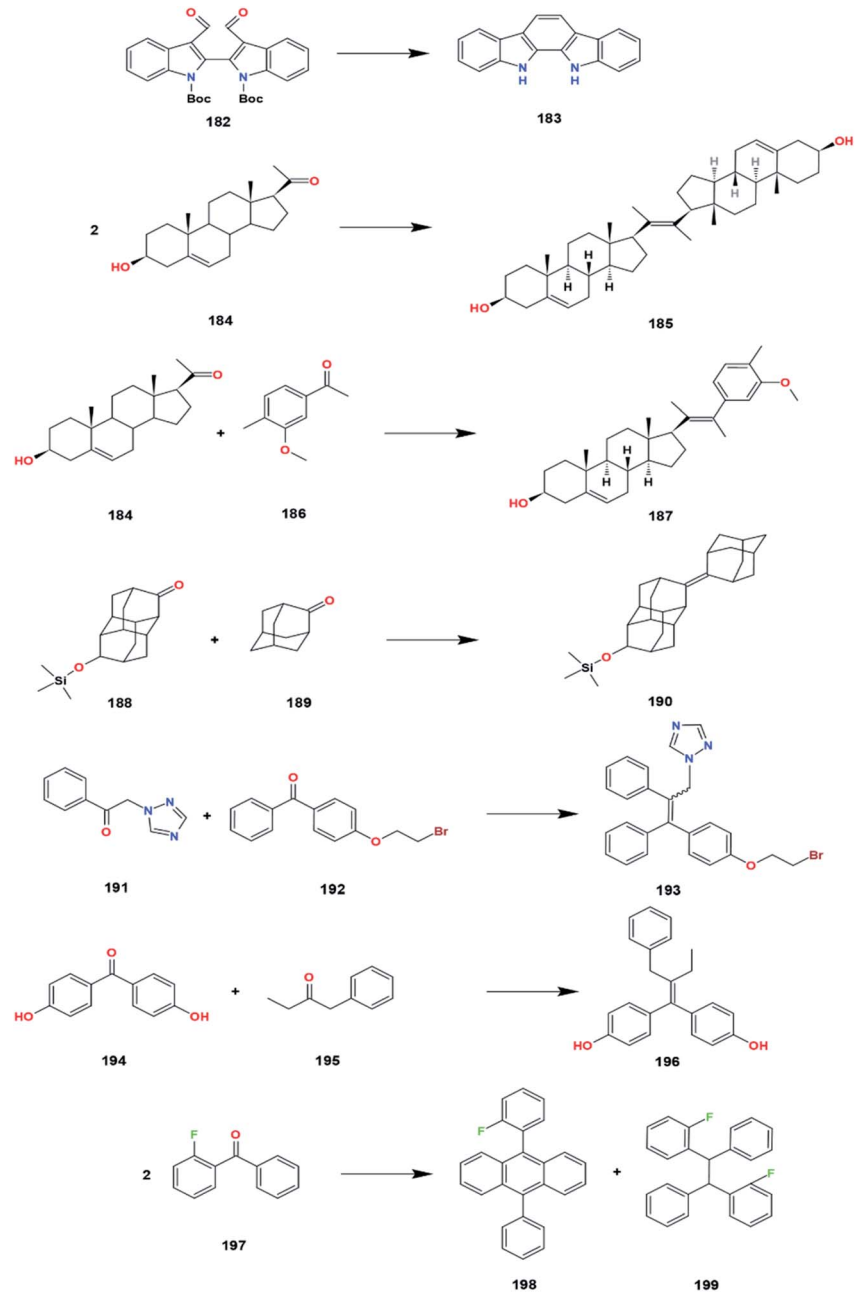

Fig. 32 Application of McMurry reaction in synthesis of natural products.

Table 24 Application of McMurry reaction in synthesis of natural products

		Reagent				Condition			
Substrate	Product	Source of metal	Reducing agent	Solvent	Additive	Reaction time (h)	Temperature (°C)	Yield (%)	Ref.
182	**183**	$TiCl_4$	Zn–Cu	THF	—	20	Reflux	65	101
184	**185**	$TiCl_4$	Zn	THF	—	16 up to 45	Reflux	74	102
184 & **186**	**187**	$TiCl_4$	Zn	THF	—	16 up to 45	Reflux	73	102
188 & **189**	**190**	$TiCl_4$	Zn	THF	Pyridine	20 up to 24	Reflux	92	104
191 & **192**	**193**	$TiCl_4$	Zn	THF	—	6	−10 up to reflux	44 ($E:Z = 3:1$)	105
194 & **195**	**196**	$TiCl_4$	Zn	THF	—	2.5	Reflux	87	106
197	**198** & **199**	$TiCl_4$	Zn	THF	Pyridine	Over-night	Reflux	30 (**198**); 45 (**199**)	107

containing aldehyde and aromatic, **163**, in the $TiCl_4$–Zn–dioxane system.[95] Further oxidation of the product, **164**, produced cyclopenta[*l*]phenanthrenes as a starting material to create large aromatic compounds or conjugated polymers.[95] Phenanthrene also belongs to the PAH group of compounds used to make dyes, pesticides, medicines, and plastics.[15] In porphycene chemistry, two β-hexaalkylated porphycenes, **166** and **169**, along with their *cis* analogues, **167** and **170**, were successfully synthesized by Pati *et al.*[96] The reaction utilized $TiCl_4$–Zn–THF mixtures with the addition of copper(I) chloride reagent. Copper halides are used to prevent the oxidation of low-valent titanium by an unpredicted oxidizing agent. The separation of *cis*- and *trans*-porphycenes derivative is quite tricky due to the absence of polarity differences. Therefore, separation is performed by repeated recrystallization. Porphycene compounds generally have relatively stable isomers due to the presence of strong intramolecular hydrogen bonds. These interactions contribute to NH tautomerism and impact the double hydrogen transfer process.[96] Another experiment related to porphycene is the synthesis of expanded porphycene containing 34 π-electrons, **172**.[97] The molecule is stable in ambient air and light due to a highly effective cyclic π-conjugation. The large conjugated pi-electron system also plays a role in stabilizing highly reactive organic radical compounds.

Cyclophane is a hydrocarbon compound containing aromatic units and aliphatic chains. The aliphatic chains serve as a bridge that connects aromatic units in a non-adjacent position. Lately, the application of the McMurry reaction in synthesizing new non-natural products from the cyclophane class, **174** (indolophanetriene) and **176** (carbazolophanetriene), has been reported.[98] Compounds belonging to the cyclophane class generally can be used as molecular recognition, information storage, and nanodevices.[98] By utilizing the McMurry reaction, the intermolecular coupling was performed successfully. Although there are two carbonyls in the same substrate, the intramolecular reaction does not occur because the positions of the two carbonyls are relatively far apart. Reductive McMurry cyclization of α,ω-(diazulen1-yl)-α,ω-diketones, **177**, permitted the formation of cycloalkenes, **178**, with pinacol and pinacolone as minor products (Table 23).[99]

An experiment conducted by Kochi *et al.* demonstrated the effectiveness of McMurry coupling to produce 1-arylbutadiene, **181**, as a photochromic compound.[100] In addition to the previously discussed application of photochromic compounds, one of the important functions of photochromic compounds in the manufacture of glasses is to prevent some objects from being exposed to UV radiation. For example, a product that applies the photochromic concept is photochromic lenses. Photochromic lenses are similar to eyeglass lenses in general when in a room with relatively low light intensity. However, these lenses may darken when exposed to sunlight. Color changes occur due to UV radiation from the sun, which has an impact on photochromic molecules. By using photochromic lenses, the eyes will be protected from direct exposure to UV light. Excessive exposure to UV B rays into the eye can cause cataracts up to permanent blindness.

7.2 Synthesis of natural products

Various applications of McMurry coupling in the synthesis of natural and related products have appeared that efficiently construct a wide variety of macromolecules (Fig. 32). A natural product is a substance or compound produced by bio-based materials, biotic materials, biological fluids, and other materials from living organisms.

The intramolecular cyclization promoted by titanium halides with reducing agents has been applied to the total synthesis of indolo[2,3-α]carbazole, **183**, that provides pharmacological effects such as antifungal, antihypertensive, antimicrobial, and anticancer.[101] Protection of the amine with boc compound increased the yield of the indolo[2,3-α]carbazole. Both amines and amides can react slowly with low valent titanium. Therefore, protection of these groups is needed to prevent the complexation of titanium to nitrogen atoms. Apart from being synthesized, indolo(2,3-*a*)carbazoles can be isolated directly from marine invertebrates (sponge, tunicate, mollusk), myxomycetes (*Arcyria ferruginea* and *Arcyria cinerea*), actinomycetes, and blue-green algae (*Nostoc sphaericum* and *Fischerella ambigua*).

In 2019, Abdul-Reda and Muhee succeeded in synthesizing pregnenolone derivatives, **185** and **187**, *via* an intermolecular coupling reaction.[102] Pregnenolone is hydrophobic with the basic structure of four hydrocarbon rings connected. Some of the functional groups present in pregnenolone consist of a ketone bonded to C_{17}, two methyls bonded to C_{13} and C_{18}, a hydroxyl bonded to C_3, and a carbon–carbon double bond at C_5. It is a main steroid synthesized from cholesterol in invertebrates and mammals that plays an essential role in producing other steroid hormones, including progesterone, estrogen, and dehydroepiandrosterone (DHEA). Pregnenolone is naturally produced in the adrenal glands, brain, and gonads.[103] Some of its derivatives are candidates for treating prostate cancer, bacterial infection, and fungal infection. Moreover, pregnenolone and its derivatives could enhance the neuroactive properties for learning and keeping memory.

In 2018, A novel synthetic of diamondoids compound, especially adamantane, **190**, has also been reached by Hoc *et al.* using the McMurry reaction.[104] Diamondoid is an unusual molecule that has been widely applied in geochemistry since 1990 due to its peculiar cage molecular structure. Both diamondoid and its derivatives are contained naturally in oil and fossil deposits with a 1–100 ppm concentration.[104] The low series of diamondoids plays a vital role in designing and synthesizing drug delivery systems. The experimental results showed that the McMurry coupling of diamantanone and amantanone was successful with high product yields.

McMurry reaction is also used as the fundamental synthetic step in preparing the precursor, **193** and **196**, to synthesize tamoxifen derivative compound as a candidate for treating breast cancer, dysmenorrhea, and gynecomastia.[105,106] Tamoxifen belongs to the triphenylethylene family that acts as a selective estrogen receptor modulator (SERM). The structure of tamoxifen was derived from estrogen (diethylstilbestrol) and antiestrogen such as chlorotrianisene. This causes tamoxifen to

have estrogen and antiestrogen activity that can work in certain parts of the body. For example, tamoxifen has a predominant antiestrogen activity in the breast area and predominant estrogen activity in the uterus.

Anthracene or green oil is a compound that can be obtained from coal tar. In the previous section, the presence of anthracene also increased the selectivity of the McMurry reaction. In 2019, the phenylanthracene core compound **198** was successfully synthesized by Akhmetov *et al.* using fluorinated benzophenone.[107] The success of these experiments opens up opportunities for fluoroorganic chemistry to be researched and studied further (Table 24).

8. Conclusions

McMurry's reaction provides an efficient way to create a new carbon–carbon bond from carbonyl compounds. Over the past 5 years, the reductive coupling of carbonyls has been widely applied to the synthesis of sophisticated and complicated molecules with fascinating optical, optoelectronic, photochromic, luminescent properties, and even diverse biological activities. Several medium and large ring systems such as PAHs, indole derivatives, carbazole derivatives, cross-linked GQD, diamondoid derivatives, and other complicated molecules have been successfully obtained through intermolecular, intramolecular, tandem coupling, and keto ester McMurry coupling reaction.

Based on the current hypothesis, the McMurry reaction adapts a heterogeneously catalysed reaction which assumes that the low-valent titanium species is a surface that interacts with oxygen on the carbonyl substrate. Further investigations are needed to confirm the number of titanium species involved on one surface during the interaction process and the manner of Ti–O bond-breaking to get a better understanding to the McMurry reaction mechanism.

Despite various applications of the McMurry reaction in recent decades, there are still some drawbacks of this reaction that should be considered. The major disadvantage of the McMurry reaction is its intolerance of easily reduced side functional groups such as allylic alcohol, 1,2-diol, nitro, sulfoxide, epoxide, halohydrin, enedione, and quinone. This problem has now been controlled by applying a low-temperature reaction method that utilizes certain additive compounds. It is essential to look for further alternatives considering there is little chance of redox reactions and diol formation occurring at low temperatures. Another way to address this problem, Asako has reviewed some recent progress in transition-metal-catalyzed deoxygenative coupling reactions under mild conditions.[22] Some of the examples are $[Ir(FCF_3\text{-}ppy)_2dtbpy]PF_6/B_2pin_2$ system and $[Rh_2(OAc)_4]$. By utilizing these catalysts, the reactions can be carried out in milder condition and increase the tolerance to easily reduced side functional groups. In addition to this problem, the development of the enantioselectivity of this reaction is necessary by considering that complicated systems are still required to obtain products with higher selectivity, causing an inefficient reaction with relatively low yields.

In summary, McMurry reaction has a lot of potentials to be applied and developed in the future. Further explorations with a different approach might be needed to verify the specific reaction mechanism, the interaction between the substrate and the reagent on a molecular basis, optimum reaction condition, and the suitability of additive with reaction. Understanding these factors may lead to discovering a modified McMurry reaction to synthesize various complicated compounds with satisfactory results and overcome the shortcomings of conventional McMurry reactions.

Author contributions

All authors contributed to the preparation of the draft. A. Bongso participated for the preparation of the original draft and graphic visualisations. R. Roswanda and Y. M. Syah contributed substantial revision for the final draft.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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