

Award Accounts

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Multisubstituted Olefins: Platform Synthesis and Applications to Materials Science and Pharmaceutical Chemistry

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The concept of platform synthesis has been successfully demonstrated as a useful strategy for making multisubstituted olefins in a programmable and diversity-oriented format. As well as applications to the synthesis of pharmaceutically important molecules such as tamoxifen and CDP840, applications to materials science, which have led to the discovery of interesting fluorescent materials and properties, are also described.

Olefin structures (C=C) are ubiquitous in organic molecules. From the well-known chemistry of vision (rhodopsin) to the emerging field of C=C-based π-conjugated materials (e.g., polyacetylenes), olefin structures have found widespread applications in our lives. In addition to their functions in their own right, olefins are useful building blocks or precursors for other functionalities in organic synthesis. Therefore, almost all textbooks of organic chemistry devote sections and chapters to the synthesis and reactions of olefins. Because of this and many other reasons, the regioselective and stereoselective synthesis of substituted olefins has been a central subject in organic synthesis.

Is there a truly general method to prepare substituted olefins? Unfortunately, the answer is likely to be "no" at present. There has been impressive development in the synthesis of monosubstituted and disubstituted olefins, but the stereoselective synthesis of multisubstituted (trisubstituted and tetrasubstituted) olefins lags far behind. In particular, the general synthesis of tetrasubstituted olefins with four different substituents has been a formidable challenge for chemists for years (Chart 1).

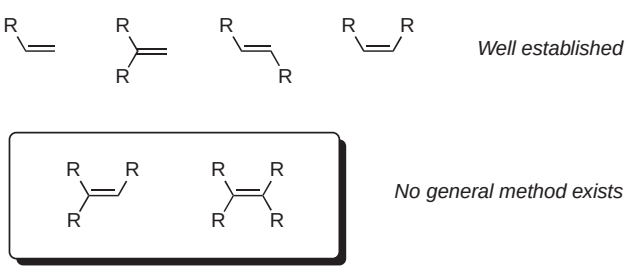

Chart 1.

Based on this background, we decided to embark on a research program directed toward a general and programmable synthesis of multisubstituted olefins. In this account article, we report on our investigations along this line as well as the application of our synthetic strategy to the synthesis of functional organic materials and pharmaceutically important molecules.

1. Olefin Synthesis

How are olefins usually synthesized? Listed in Fig. 1 are three representative types of olefin synthesis: (1) elimination from alkanes, (2) addition to alkynes, and (3) substitution of alkenes. Many of the reported olefin syntheses fall into this

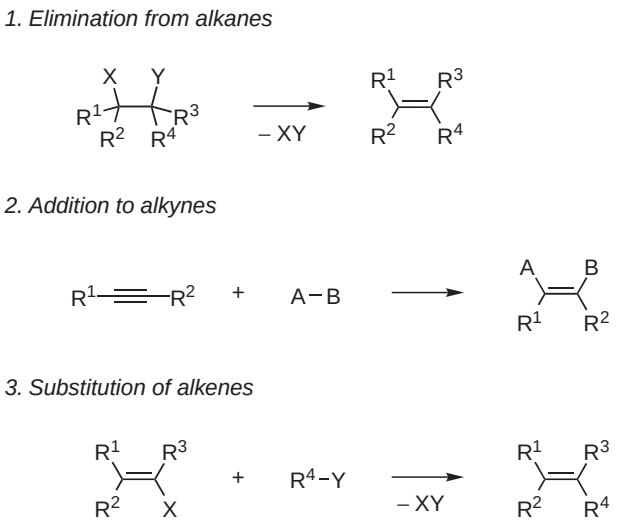

Fig. 1. Three representative types of olefin synthesis.

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categorization.[1] For example, Hofmann elimination, Cope elimination, β-elimination from sulfoxide or selenoxide, the Burgess dehydration reaction, and Corey–Winter olefination all fall into category 1. The olefination reactions that involve such a 1,2-elimination step are the Wittig reaction, Horner–Wadsworth–Emmons reaction, Peterson reaction, Tebbe olefination, Knoevenagel condensation, Julia–Lythgoe olefination, Takai–Utimoto olefination, and McMurry coupling. Transition metal-catalyzed hydrometalation, dimetalation, and carbometalation reactions to alkynes fall into category 2. The selective reduction of alkynes to alkenes mediated by H_2/Pd/$CaCO_3$/PbO or Na/NH_3 also falls into this category. The representative reaction that falls into category 3 is the metal-catalyzed cross-coupling reaction where halides or metals on C=C are substituted by a suitable coupling partner under the influence of a metal catalyst. The metal-mediated C–H functionalization of alkenes is a more direct olefination of this class. The palladium-catalyzed Mizoroki–Heck-type C–H arylation and alkenylation may fall into such an olefination, although the mechanism involves an addition/elimination sequence similar to category 1. Although not falling into any of these categories, metal-mediated alkene metathesis reactions are also useful methods for creating the C=C structure.

These reactions have enjoyed widespread applications in organic synthesis as exemplified by natural product synthesis.[1,2] However, all of these reactions are far from being truly general methods for substituted olefins, unfortunately. A tuning of reaction conditions might result in the selective synthesis of one of the possible isomers, but the synthesis of all possible isomers is almost impossible with these conventional methods.

2. Platform Synthesis: A New Concept

Based on the background, we envisaged that sequential assembly (installations) of components onto a C=C core of a suitable ethylene derivative (platform) would be a straightforward strategy for multisubstituted olefin synthesis (Fig. 2). This strategy may be regarded as a strategic integration of category 3 olefinations. The simplest platform in this strategy might be ethylene (CH_2=CH_2). However, the selectivity associated with C–H functionalization (regioselectivity and stereoselectivity) would be dependent on the existing substituents; therefore, this is not suitable as a platform. Although such a selective functionalization would be possible when an ethylene derivative having four chemically distinguishable elements [$E^1(E^2)C$=$CE^3(E^4)$] is used as a platform, the selective synthesis of such a platform itself would be another challenge.

In view of synthetic flexibility, ethylene derivatives substituted by a suitable element (vinyl-element compounds: CH_2=CH–E) are potentially powerful "multifunctional" platforms for multisubstituted olefins (Fig. 2). Due to the presence of such an element (E), the three C–H bonds (one α-C–H and two β-C–H bonds) and the C–E bond are non-equivalent, thereby distinguishable in principle in component-assembling reactions. Therefore, the site-selective and stepwise installation of components at these bonds should result in an extremely flexible and diversity-oriented[3] synthetic route toward multisubstituted olefins. Although conceptually intriguing, such an approach has been rather unexplored because of the apparent difficulty in controlling the reactivity at the desired bonds.

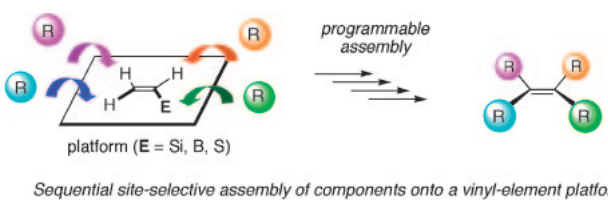

Fig. 2. Platform strategy for multisubstituted olefin synthesis.

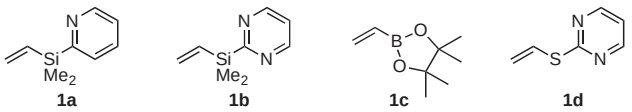

Fig. 3. Vinyl-element platforms for multisubstituted olefin synthesis developed in our laboratory.

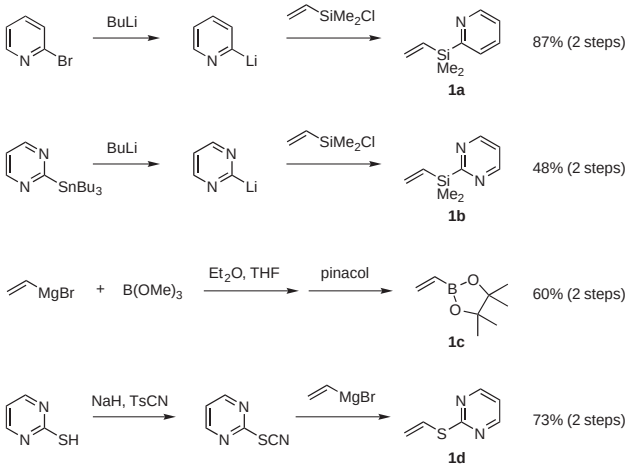

Fig. 4. Synthesis of vinyl-element platforms.

We developed four vinyl-element compounds, **1a**–**1d**, realizing our concept (Fig. 3). Their syntheses are shown in Fig. 4. As can be seen from the structures shown in Fig. 3, we often append catalyst- or reagent-directing groups such as a pyridyl group onto a linker element.[4] The presence of these groups permits a number of metal-mediated component-assembling reactions that are essentially unattainable without such groups. Thus, the use of directing groups is extremely advantageous in revealing the full potential of vinyl-element compounds as platforms, although the "reactivity differentiation" benefits from the inherent and strong stereo-electronic bias exerted by a suitably positioned element (E). Thus, an orchestrated interplay of organo-element chemistry and coordination chemistry is the essence of our approach.

3. Platform Synthesis of Multisubstituted Olefins

General Synthetic Scheme. The general synthetic scheme for multisubstituted olefins using vinyl-element compounds **1a**–**1d** as platforms is shown in Fig. 5. Common to all vinyl-element platforms, we utilize the Pd-catalyzed Mizoroki–Heck reaction[5] as a component installation method at the β-C–H bond (**1** $\rightarrow$ **2**). By appending a catalyst-directing group on a linker element, a hard-to-achieve double Mizoroki–Heck reaction[6] is accomplished (**1** $\rightarrow$ **2** $\rightarrow$ **3**), which allows us to install two aryl groups at the two β-C–H bonds in a one-pot reaction.

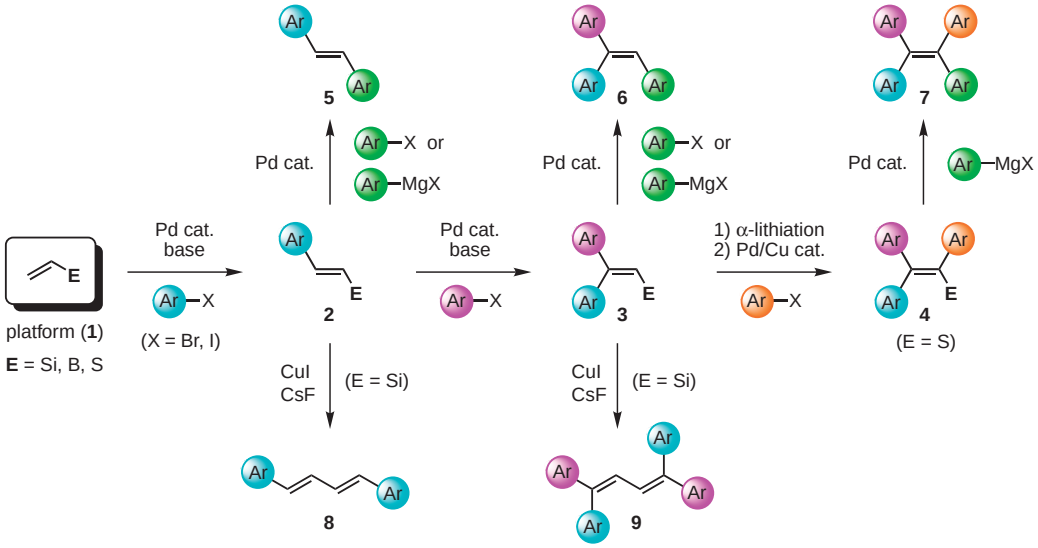

Fig. 5. General synthetic scheme for multisubstituted olefins using vinyl-element compounds **1a**–**1d** as platforms.

The successive installation of an aryl group at the α-C–H bond can be achieved by the α-lithiation of **3** with *t*-BuLi and a subsequent cross-coupling reaction[7] with an aryl halide in the presence of $Pd(PPh_3)_4$/CuI catalyst. This procedure provides **4** in high yields with virtually complete retention of stereochemistry, although it works well only for the vinyl sulfide platform **1d** at present. The final cross-coupling reaction[7] of those alkenyl-element compounds **2**–**4** results in the production of multisubstituted ethenes. Whereas Grignard reagents are used for alkenyl sulfides, aryl halides are used for alkenylsilanes and alkenylboronate esters for cross-coupling reaction. We also developed an efficient method for the homo-coupling reaction of alkenylsilanes **2** and **3** using CuI and CsF as promoters for the synthesis of multisubstituted butadienes **8** and **9**. The details are described in the following sections.

Vinylsilane Platforms. The first breakthrough in our research program was the finding that the 2-pyridyl group on silicon greatly accelerates the Mizoroki–Heck reaction of vinylsilane.[8] It is already known that there are several difficulties in this process.[9] For example, the treatment of trimethyl(vinyl)silane with aryl halide in the presence of $Pd(OAc)_2$, PPh_3, and triethylamine (typical reaction conditions) affords exclusively the styrene derivative as a result of carbon–silicon bond cleavage.[10] We expected the occurrence of the Mizoroki–Heck reaction of vinylsilane by simply appending a catalyst-directing 2-pyridyl group on silicon[11] due to the complex-induced proximity effect (CIPE).[4,12]

This concept works. In the presence of a palladium catalyst and a base, the Mizoroki–Heck reaction of **1a**[13] with aryl halides smoothly took place giving the β-substituted vinylsilanes **2a** in high yields (Fig. 6).[8] As for supporting ligands on palladium, P(2-furyl)$_3$,[14] P(*t*-Bu)$_3$,[15] and P[OC$_6$H$_3$(*t*-Bu)$_2$-2,4]$_3$[16] were found to be effective. It is reasonable to assume that the suitably positioned nitrogen atom of the pyridyl group accelerates the rate-determining C=C π-complexation and successive carbopalladation (insertion) events in the Mizoroki–Heck reaction (Fig. 6).[17] The occurrence of pyridyl-to-palladium coordination was demonstrated by ^{1}H NMR and X-ray crystal structure analysis of some key palladium complexes.[17] In line with

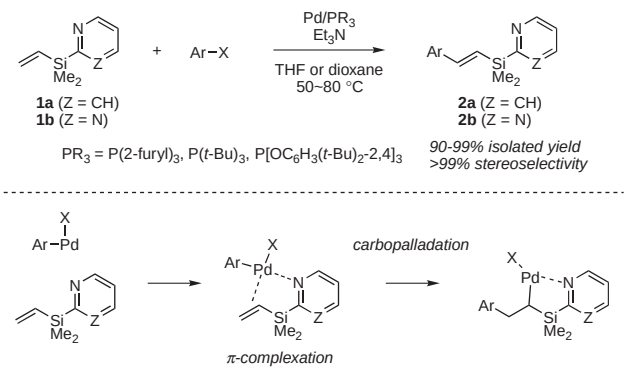

Fig. 6. Mizoroki–Heck reaction of vinylsilanes.

such a directed reaction scenario, the structurally similar 2-pyrimidyl(vinyl)silane **1b** was also found to be a good substrate for the Mizoroki–Heck reaction.[18] The stereoselectivity was in agreement with the commonly assumed mechanism (stereospecific *syn* carbopalladation and *syn* β-hydrogen elimination).[5] Noteworthy features of this process are that (i) the formation of styrene (C–Si bond cleavage) was completely suppressed, (ii) the coupling occurred under mild conditions (50 °C) and at low catalyst loading (as low as 0.1 mol %), (iii) virtually complete stereoselectivity (>99% *E*) was observed, and (iv) coupling occurred with a wide array of electronically and structurally diverse aryl, heteroaryl, and alkenyl halides.

Subsequently, we found that the hard-to-achieve double Mizoroki–Heck reaction can also be achieved with these vinylsilanes (**1** → **2** → **3**; Fig. 7).[17] Previously, such a process had been known to be extremely sluggish; therefore, such doubly arylated products are usually prepared by stepwise reactions.[19] The stereoselectivity was again found to be virtually complete. The second aryl group always occupies a position *trans* to the silyl group, which is in agreement with *syn* carbopalladation and *syn* β-hydrogen elimination.[5] Nevertheless, this double Mizoroki–Heck reaction allows us to install two aryl groups at the two β-C–H bonds in a one-pot reaction. Representative β,β-diaryl(vinyl)silanes **3a** and **3b** prepared by this procedure

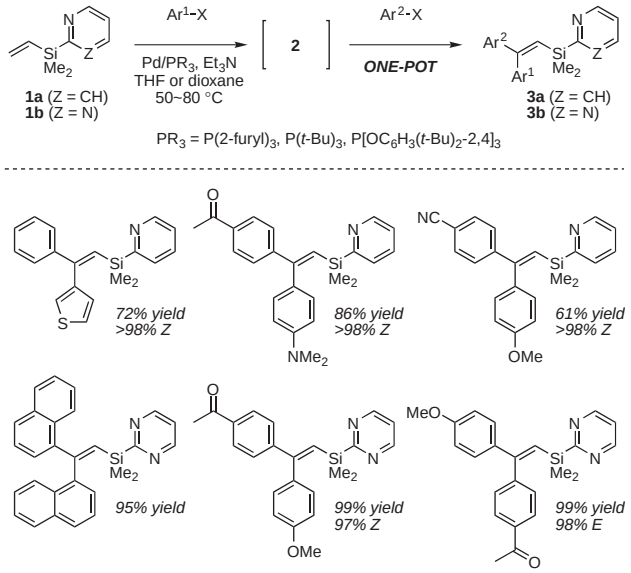

Fig. 7. One-pot double Mizoroki–Heck reaction of vinylsilanes.

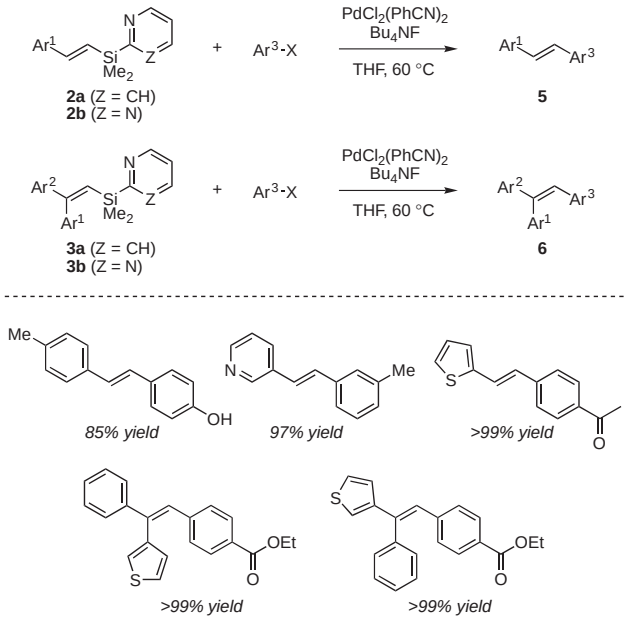

Fig. 8. Hiyama-type silicon-based cross-coupling reaction of alkenylsilanes.

are shown in Fig. 7.[17,18] Although not described herein, this one-pot double Mizoroki–Heck reaction proceeds smoothly with α-substituted 2-pyridyl(vinyl)silanes as well.[17]

Having established the Mizoroki–Heck-type double C–H arylation of vinylsilanes, we next turned our attention to C–Si arylation by means of palladium catalysts (Hiyama-type silicon-based cross-coupling reaction).[20] We initially screened various palladium complexes to accomplish the cross-coupling reaction of alkenyl(2-pyridyl)silanes with aryl halides, but the only product detected was the Mizoroki–Heck-type arylation product. This may have been due to the strong directing effect of the pyridyl group and the poor transmetalation ability of silicon. However, by adding Bu_4NF the course of the reaction changed to the C–Si arylation manifold and the C–H arylation

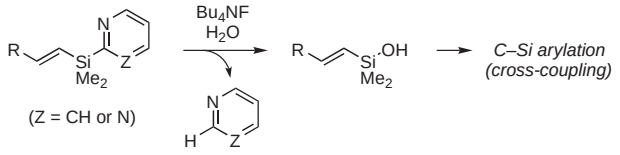

Fig. 9. A plausible pathway for Hiyama-type coupling of alkenylsilanes.

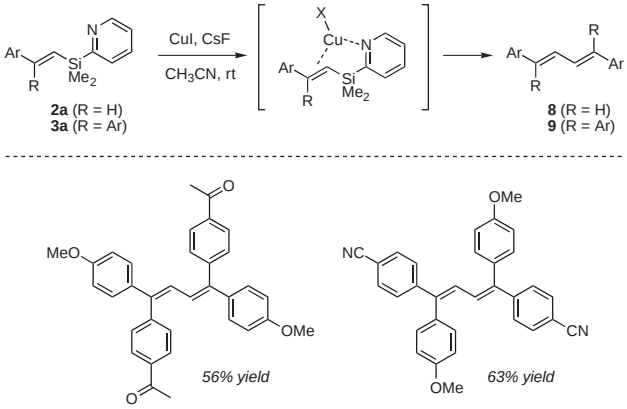

Fig. 10. Cu-mediated homo-coupling reaction of alkenyl(2-pyridyl)silanes.

manifold was completely suppressed (Fig. 8).[21] Similarly, alkenyl(2-pyrimidyl)silanes undergo cross-coupling reaction with the Pd/Bu_4NF system.[18] In this transformation, a phosphine-free complex such as $PdCl_2(PhCN)_2$, $PdCl_2(CH_3CN)_2$, or $[PdCl(allyl)]_2$ was found to be active. Gratifyingly, the cross-coupling reaction of arylated vinylsilanes **2a**, **2b**, **3a**, and **3b** proceeds with various electronically and structurally diverse aryl halides to afford diarylethenes **5** and triarylethenes **6** in good to excellent yields.[17] Representative products that were prepared are shown in Fig. 8. The reactions proceed with virtually complete retention of stereochemistry. As for a plausible mechanism for the complete switch of reaction pathway (C–Si arylation vs C–H arylation), we found that the pyridyl group and pyrimidyl group on silicon, which act as directing groups for Mizoroki–Heck-type arylation, are selectively removed from silicon to generate alkenylsilanols, which are known to be highly active in cross-coupling reaction (Fig. 9).[21,22]

In addition to cross-coupling reaction (C–Si arylation), we developed the homo-coupling reaction of alkenyl(2-pyridyl)-silanes **2a** and **3a** mediated by CuI and CsF (Fig. 10).[23] Virtually complete retention of stereochemistry during the homo-coupling reaction was observed. With this method in hand, 1,3-butadienes with two or four electronically varied aryl groups (**8** and **9**) can be prepared very efficiently. Interestingly, we also found a strong promoting effect of the 2-pyridyl group on silicon in this homo-coupling reaction; no reaction takes place with alkenyl(phenyl)silanes. The mechanistic studies indicated that the suitably positioned pyridyl group should help the C=C bond to coordinate to copper through precoordination and/or vinyl-N chelation, thereby allowing subsequent Si-to-Cu transmetalation to proceed very efficiently. Such a strong vinyl-N chelation was observed in the X-ray crystal structure of key alkenyl(2-pyridyl)silane–CuX complexes.[23]

Vinylboronate Platform. The above mentioned chemistry

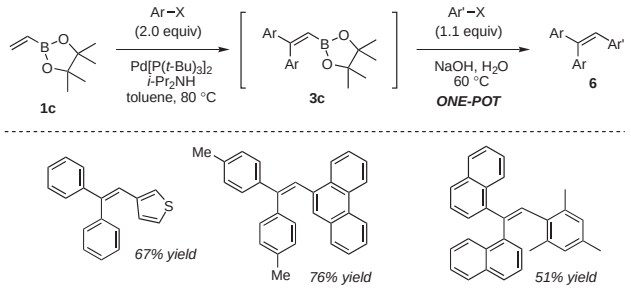

Fig. 11. One-pot synthesis of triarylethenes using **1c** as a platform.

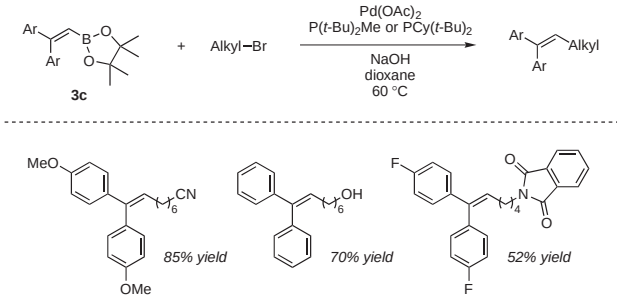

Fig. 12. Platform synthesis of 1,1-diaryl-1-alkenes.

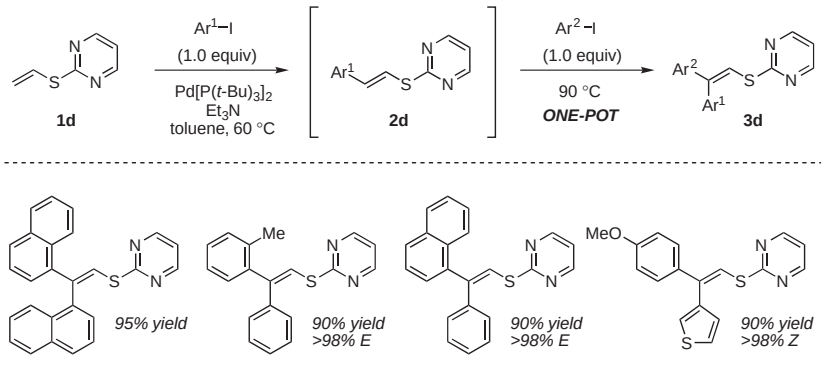

Fig. 13. One-pot double Mizoroki–Heck reaction of 2-pyrimidyl vinyl sulfide **1d**.

of 2-pyridyl(vinyl)silane and 2-pyrimidyl(vinyl)silane can be regarded as a proof-of-principle of our platform strategy for multisubstituted olefin synthesis. However, the one-pot integration of all component-assembling reactions (double Mizoroki–Heck reaction and cross-coupling reaction) is not possible with the silicon-based method. Toward this end, we embarked on the use of a vinylboron compound as the platform.[24] After extensive screening of conditions, we found that the catalyst/base combination of $Pd[P(t\text{-}Bu)_3]_2/i\text{-}Pr_2NH$ is particularly effective for the double Mizoroki–Heck reaction of vinylboronate pinacol ester **1c** (Fig. 11).[25] Moreover, we found that by simply adding aryl halides, NaOH, and H_2O to the reaction mixture of the double Mizoroki–Heck reaction, triarylethenes **6** could be obtained in good overall yields (Fig. 11). Heteroaryl halides as well as sterically hindered aryl halides can also be used. The representative triarylethenes **6** prepared by this method are shown in Fig. 11.[25]

In our multisubstituted olefin synthesis using vinylsilane or vinylboronate as a platform, substituents such as aryl, heteroaryl, and alkenyl groups are efficiently introduced, due mainly to the high reactivity of organic halides bearing those groups in metal-catalyzed coupling reactions.[5,7] However, the utility of our strategy would be substantially enhanced if we could extend the scope of introducible organic groups. Very recently, we established a protocol for introducing alkyl groups in the final cross-coupling reaction, which led to a straightforward synthesis of pharmaceutically important 1,1-diaryl-1-alkene structures (Fig. 12).[26,27]

Vinyl Sulfide Platform. Our efforts toward a general synthesis of multisubstituted olefins have led to the emergence of 2-pyridyl(vinyl)silane **1a**, 2-pyrimidyl(vinyl)silane **1b**, and vinylboronate pinacol ester **1c** as useful platforms for trisubstituted olefins and tetrasubstituted butadienes. However, there still clearly remained an important and most challenging subject in our research program, namely, establishing a general protocol for tetrasubstituted olefins. Although there exist methods for the synthesis of tetrasubstituted olefins, a procedure that allows the preparation of all possible isomers in a programmable format has not yet been reported. Gratifyingly, our search for an alternative vinyl-element platform led to the discovery of 2-pyrimidyl vinyl sulfide **1d** as a first-generation platform permitting the programmable synthesis of tetrasubstituted olefins (Figs. 13–15).[28]

As a component-installing method at the β-C–H bond of vinyl sulfide, we again investigated the Pd-catalyzed Mizoroki–Heck reaction.[5] Since there is only one example in the literature, possibly reflecting the low reactivity of vinyl sulfide toward the Mizoroki–Heck reaction,[29] we began by searching for a highly reactive vinyl sulfide as well as a catalyst. After extensive screening, we found that appending a catalyst-directing 2-pyrimidyl group on sulfur tremendously enhances the reactivity of vinyl sulfide toward the Mizoroki–Heck reaction.[28] In addition, we found the $Pd/P(t\text{-}Bu)_3$ system[15] to be a highly active catalyst in our synthesis. Moreover, due to the presence of the catalyst-directing 2-pyrimidyl group on sulfur, the hard-to-achieve double Mizoroki–Heck reaction has been accomplished, which allows us to install two aryl groups at the two β-C–H bonds in a one-pot reaction with virtually complete stereoselectivity (Fig. 13). The yields were greater than 90% in most cases, even when using equimolar quantities of each reagent.[28]

Having established an efficient aryl-installing method at β-

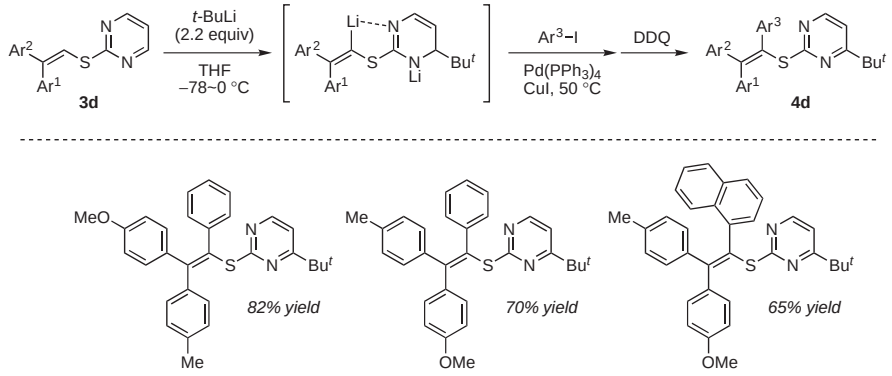

Fig. 14. α-Lithiation/cross-coupling reaction of alkenyl 2-pyrimidyl sulfides **3d**.

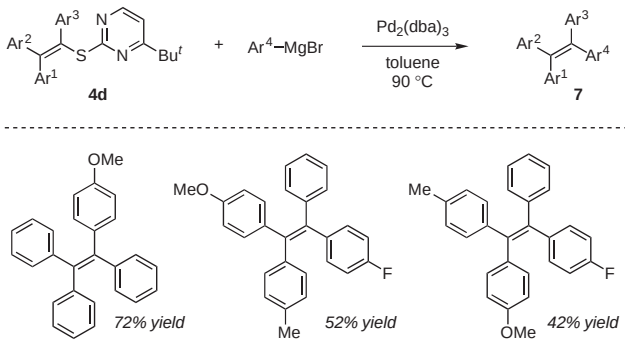

Fig. 15. Synthesis of tetraarylethenes **7** through cross-coupling reaction.

C–H bonds, we next embarked on the assembly of a third aryl group at the α-C–H bond of **3d**. Such a process had not been accomplished with alkenylsilanes **3a** and **3b** and alkenylboronates **3c**. After many experiments, we found that this could be achieved by the α-lithiation/cross-coupling sequence of **3d** (Fig. 14). Thus, a THF solution of **3d** was treated with *t*-BuLi (2.2 equiv) to afford the α-lithiated species with the *t*-butyl group installed onto the pyrimidine ring.[30] The successive installation of an aryl group was accomplished by a cross-coupling reaction of the thus-obtained organolithiums with aryl halides under the influence of $Pd(PPh_3)_4$/CuI catalyst. The use of a Cu co-catalyst is essential in this cross-coupling reaction. The treatment of the resultant crude solution with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) resulted in the regeneration of the pyrimidine ring (oxidation)[31] to finally provide triarylated vinyl sulfides **4d** in good yields with virtually complete retention of stereochemistry (Fig. 14).[28]

For the final aryl-assembling method at the remaining C–S bond of triarylated vinyl sulfides **4d**, we found that cross-coupling reaction with Grignard reagents (Ar^4MgBr) in the presence of Pd catalyst was effective (Fig. 15).[32] A number of tetraarylethenes **7** were produced in moderate to good yields with virtually complete retention of stereochemistry (Fig. 15).[28] Noteworthy features are that (i) all aryl groups assembled can be derived from readily available aryl halides or their Grignard reagents, (ii) installation at desired positions can be achieved by the addition of aryl halides in the appropriate order, and (iii) simple alteration of the addition order in the sequence results in the production of all possible isomers of tetraarylethenes.

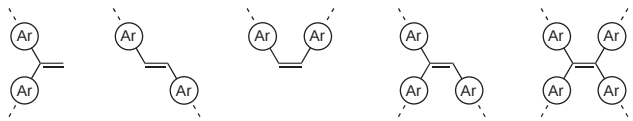

Fig. 16. Arylethene-based extended π-systems.

4. Rapid and Systematic Construction of Triarylethene-Based Extended π-Systems

The carbon–carbon double bond (C=C) is a minimal unit in π-systems. Therefore, an extended π-system equipped with π-systems such as aryl groups on a minimal π-unit, C=C (arylethene-based extended π-system), would be an interesting target as a functional material (Fig. 16). Although some of the π-systems within this family, such as stilbene derivatives and poly(arylenevinylene)s (1,2-diarylethene-based π-systems), have already established their utility as functional materials,[33] an important objective still remains in this class of extended π-systems. More specifically, exploring the chemistry (synthesis and properties) of π-systems based on a highly substituted C=C core (triarylethene- and tetraarylethene-based extended π-systems) remains.

General Synthetic Scheme for Triarylethene-Based Extended π-Systems. The platform synthesis of multisubstituted olefins described in the previous section represents a new strategy that permits assembly of π-systems, such as aryl groups, onto a C=C core (minimal π-unit) in a programmable and diversity-oriented format. Because aryl-assembling sites are programmed in our synthesis, the strategic use of bifunctional or trifunctional aryl units (ArX_2 or ArX_3) in place of a monofunctional unit (ArX) in the reaction sequence described in Fig. 5 results in the selective and systematic production of various types of triarylethene-based extended π-systems, which would otherwise be difficult to construct (Fig. 17).[18,25] As platforms for this study, we used vinylsilanes **1a** and **1b** and vinylboronate **1c**.

For example, the treatment of **3** (double Mizoroki–Heck reaction product of **1**) with ArX_2 in the presence of Pd catalyst results in the production of the interesting extended π-system **14**. The use of trifunctional aryl units is also interesting. For example, when ArX_3 are used in the final cross-coupling reaction with **3**, the starburst π-system **15** can be prepared with ease. When the sequence is performed using the addition order $ArX/ArX_2/ArX$ and $ArX_2/ArX/ArX$, extended π-systems with interesting structures (**16** and **17**) are selectively pro-

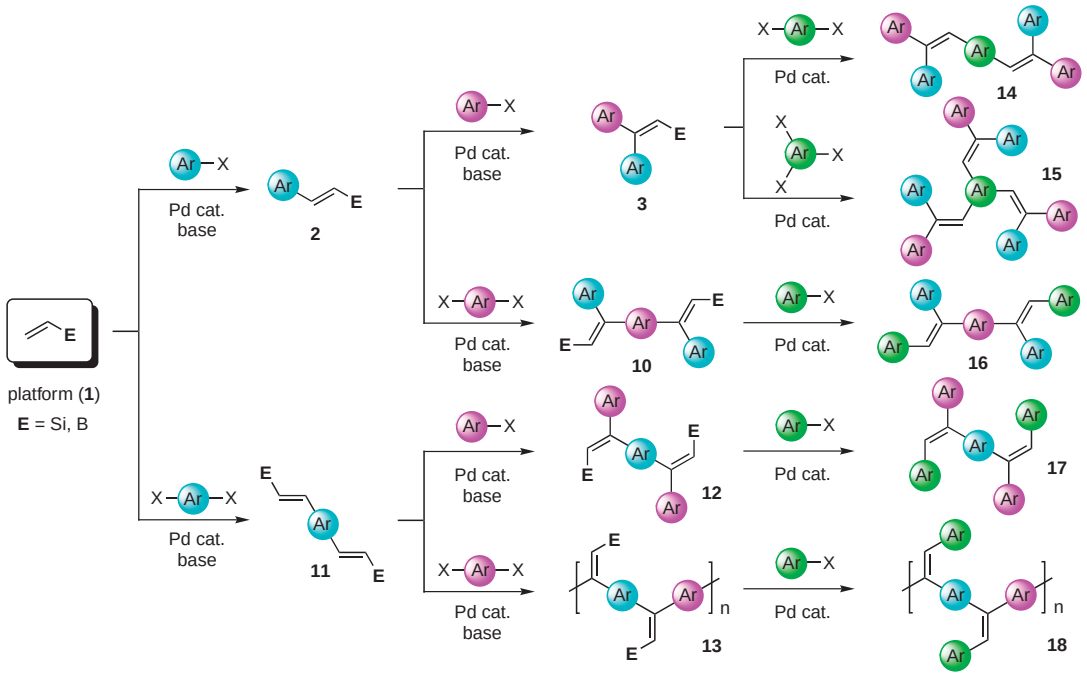

Fig. 17. Systematic construction of triarylethene-based extended π-systems.

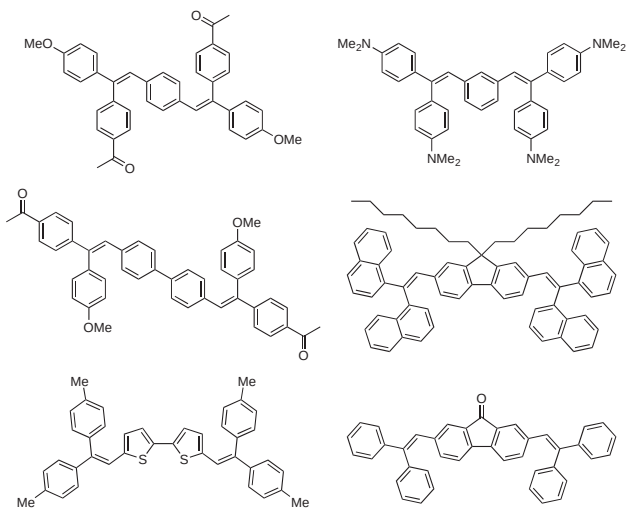

Fig. 18. Representative π-systems **14**.

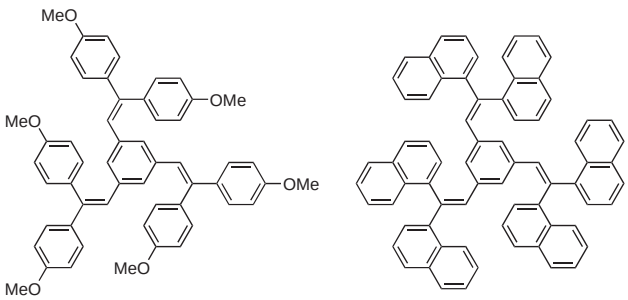

Fig. 19. Representative starburst π-systems **15**.

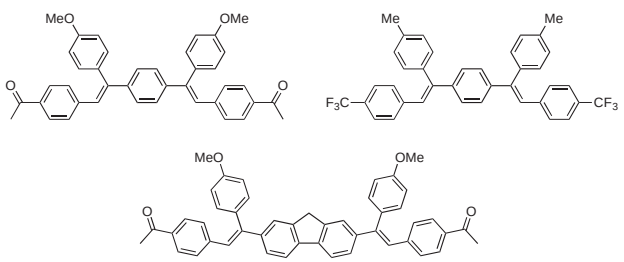

Fig. 20. Representative π-systems **16**.

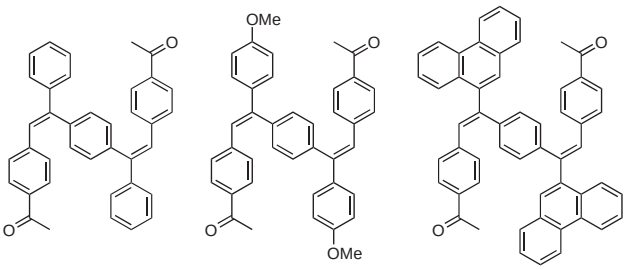

Fig. 21. Representative π-systems **17**.

duced. Moreover, when a double Mizoroki–Heck reaction is performed with ArX_2 alone, an unprecedented type of polymerization takes place. The successive cross-coupling reaction with ArX then affords the novel cross-conjugated polymer **18**, which is otherwise difficult to construct. The power of this synthetic strategy is apparent, as all of these extended π-systems can be selectively prepared at will by using common platforms (**1**), common reactions (Mizoroki–Heck reaction and cross-coupling reaction), and common reagents (aryl halides). The representative extended π-systems **14**–**18** that have been prepared are shown in Figs. 18–22.

5. Photophysical Properties of Extended π-Systems Based on the Multisubstituted Olefin Structure

The multisubstituted olefins (arylethene-based extended π-systems **5**–**9** and **14**–**18**) prepared by the methods described

in Figs. 5 and 17 are listed in Fig. 23. Over 150 compounds were prepared in reasonable overall yields with virtually complete regioselectivity and stereoselectivity. Interestingly, many of these π-systems were found to be fluorescent. Consequently, we succeeded in making a novel chemical library of fluorescent molecules (Fig. 23).

Pictures of the fluorescent behavior of the representative π-systems upon irradiation with light at 365 nm ($CHCl_3$ solution) are shown in Fig. 24. Fluorescence color variations over a wide range of wavelengths (blue to red) were realized. It was found that the emission color as well as fluorescence quantum yields depended significantly on the attaching sites and the nature of the aryl groups attached.[18,23,25]

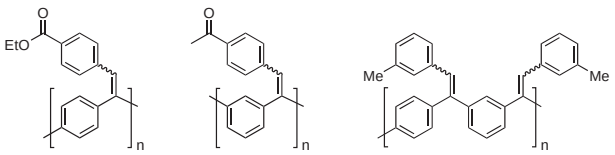

Fig. 22. Representative cross-conjugated polymers **18**.

Discovery of Efficient Blue-Emitter and Rapid Structure–Property Relationship Analysis. Our synthetic strategy described in Fig. 17 can easily be applied to the preparation of derivatives of DPVBi **14a**,[34] which has been used as a blue-emitter in organic electroluminescence devices.[18,25] Fortunately, our library-based approach within this class of π-system led to the discovery of the strong blue-emitting material **14d** (Fig. 25).[25] Its fluorescence quantum yield ($\Phi_F = 0.90$ in $CHCl_3$) is 15 times higher than that of DPVBi **14a** ($\Phi_F =$

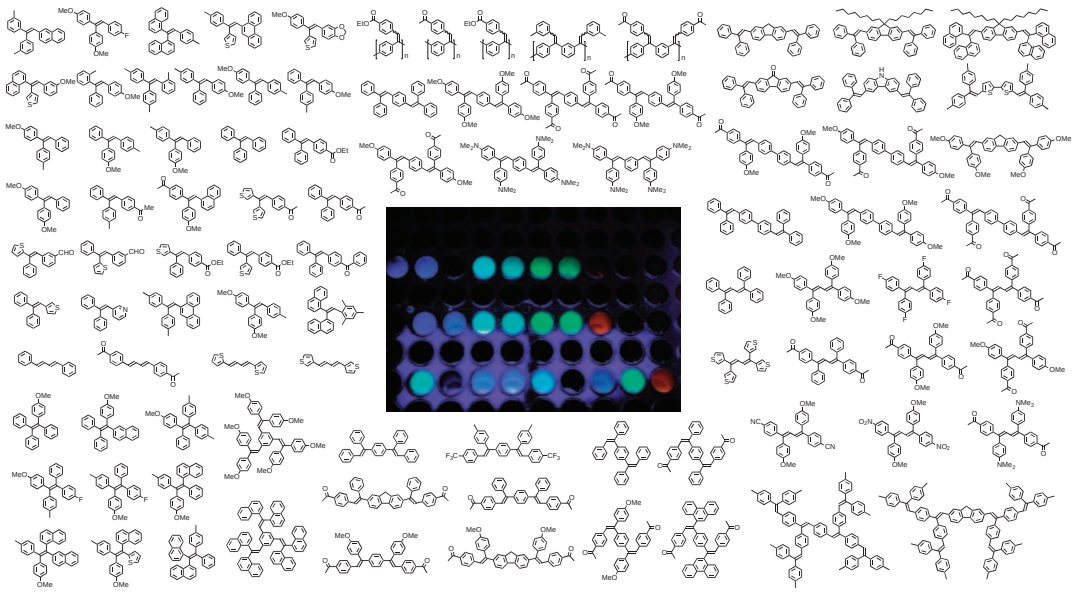

Fig. 23. Library of fluorescent multisubstituted olefins.

Fig. 24. Representative fluorescent materials found in our library.

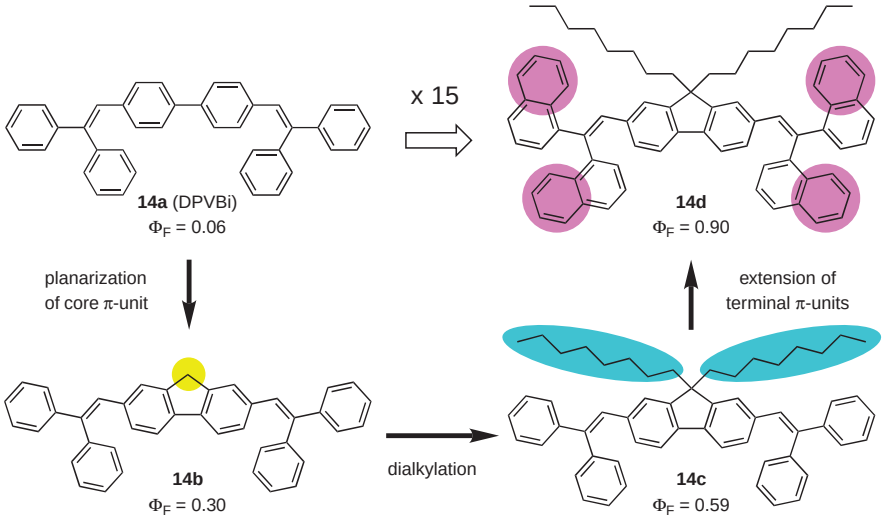

Fig. 25. A structure–property relationship analysis with regard to fluorescence efficiency.

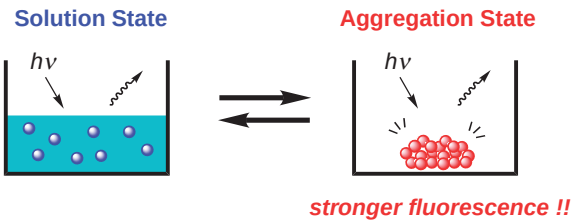

Fig. 26. Aggregation-induced enhanced emission.

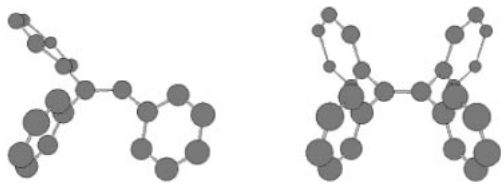

Fig. 27. Optimized structures of triphenylethene (left) and tetraphenylethene (right) obtained by PM3 calculations.

0.06). Along with the discovery of highly fluorescent materials, the rationalization of properties is also important in materials science, although not necessarily easy. We found that the systematic alteration of structures within this family of π-systems (**14a** → **14b** → **14c** → **14d**) could provide us a clue regarding the 15-fold increase in fluorescence quantum yields from **14a** to **14d** (Fig. 25).[25] From this structure–property relationship analysis, it may be possible to assume that the significant increase in fluorescence efficiency is attributed to several factors rather than any single one. We believe that the highly flexible and diversity-oriented nature of our method made such rapid analysis possible. These aspects of our synthesis should be advantageous because the accumulation of such structure–property relationships will be extremely important for future property design.

Aggregation-Induced Enhanced Emission. During the course of our investigation of photophysical properties, we found that the fluorescence efficiency of arylethene-based extended π-systems generally (and dramatically in many cases) increased in the solid state (Fig. 26).[18,35–43] For example, as well as highly fluorescent **14**, otherwise nonfluorescent π-systems such as **15** and **16** also became fluorescent in the solid state. The λ_{max} values of the solid-state emission were found to be similar to those obtained in chloroform solution. Currently, we assume that this interesting fluorescence property of arylethene-based extended π-systems is mainly attributable to their unique structure. Based on the X-ray crystal structure analysis[28] and calculations (Fig. 27), we found that these π-systems adopt a nonplanar structure due to the sterically congested environment around the C=C core. We suppose that such structural features would reduce the probability of effective intermolecular fluorescence-quenching interactions even in the solid state. If this is the case, aggregation (solidification) should lead to a reduction in the probability and amplitude of molecular motions such as twisting and out-of-plane bending motion, which might trigger radiationless transitions, thereby enhancing the fluorescence efficiency as a whole.

Such an aggregation-induced enhanced emission[35–43] was also found during the measurements of the photophysical properties of arylethene-based π-systems in dioxane/water mixtures. The following example of **14e** is typical (Fig. 28).[18] The π-system **14e** exhibited an extremely low fluorescence quantum yield ($\Phi_F = 9.3 \times 10^{-3}$) in pure dioxane. Although **14e** showed similar Φ_F values in up to a 50% volume fraction of water, we observed an obvious and drastic increase in the Φ_F values from a 60% volume fraction of water. In particular, the Φ_F value at this composition (dioxane/water = 40/60) was 46 times and 70 times higher ($\Phi_F = 0.42$) than that in pure dioxane and chloroform, respectively (Fig. 28).

The aggregation seems to be responsible for this dramatic increase in fluorescence efficiency. The formation of molecular aggregates was also indicated from the observation that the mixtures containing greater than a 60% volume fraction of water exhibited an off-white turbidity due to light scattering. Dynamic light scattering (DLS) experiments on the suspension of **14e** in a 20/80 dioxane/water mixture revealed the presence of molecular aggregates with an average diameter of 240 nm. The shape of the nanoparticles (nanoaggregates) was observed by field emission scanning electron microscopy (FE-SEM). The FE-SEM images in Fig. 29 show that the diameter of

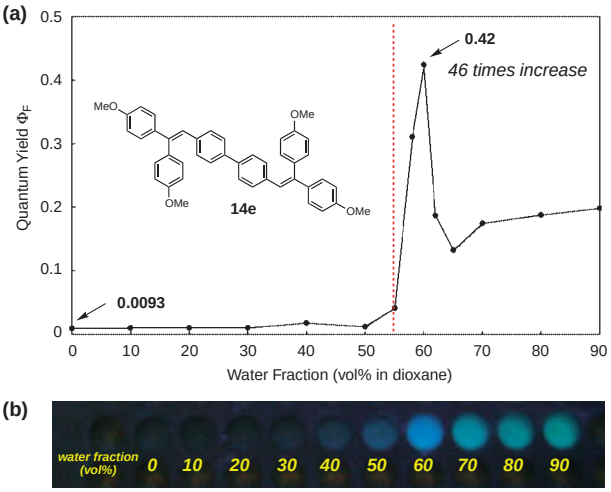

Fig. 28. (a) Fluorescence quantum yields (Φ_F) of **14e** depending on water fractions in dioxane. (b) The emissive behaviors of **14e** in dioxane/water mixtures under irradiation of light at 365 nm.

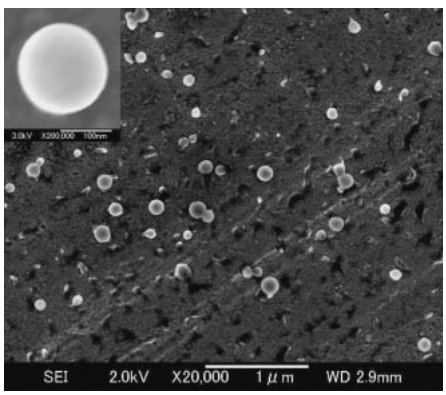

Fig. 29. FE-SEM images of nanoparticles obtained from a suspension of **14e** in a 20/80 dioxane–water mixture (bar = 1 μm). Inset shows the magnified FE-SEM image (bar = 100 nm).

the nanoparticles is in the range of 100–250 nm, which agrees roughly with that determined by DLS experiments.[18]

A Rapid Synthesis/Evaluation Process. Through this study, we mainly focused our efforts on the conventional "one-at-a-time" synthesis/purification/evaluation process because the properties of π-systems that we dealt with were largely unknown. However, after obtaining a clearer picture of the photophysical properties of these π-systems, we are now in a position to take full advantage of the programmable and diversity-oriented nature of our synthetic strategy to detect fluorescent "hits" more rapidly.[44]

For example, the 20 compounds (**14**) with five-varied aryl groups were synthesized in a parallel fashion (Fig. 17) and were then placed in a microtiter plate directly from crude reaction solutions. Irradiation of this plate (at 365 nm) allowed us to quickly detect several fluorescent compounds from this crude library, as can be clearly seen from the picture in Fig. 30. The emission color as well as relative emission efficiency was found to correlate with those of isolated samples. It should be noted that the five highly fluorescent π-systems found in the previous study were correctly detected by this method (Fig. 30).[18] Although the conventional "one-at-a-time" synthesis/purification process is necessary for the distinct evaluation of properties, this process would be extremely useful as a first-round qualitative screening method.

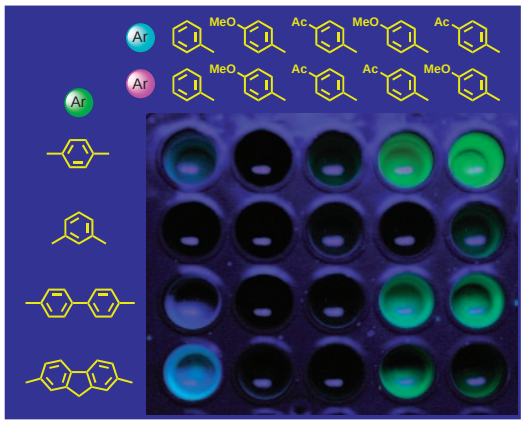

Fig. 30. Rapid synthesis and property evaluation in the extended π-system **14**.

6. Platform Synthesis of Tamoxifen-Type Tetrasubstituted Olefins

We have been interested in multisubstituted olefins not only because of their potential applications in materials science but also because of the existence of pharmaceutically important molecules of this class as exemplified by tamoxifen, an important anti-breast-cancer drug in clinical use.[45]

We have developed a general synthetic scheme for tamoxifen-type tetrasubstituted olefins using alkynyl(2-pyridyl)silane **19** as a platform (Fig. 31).[46] Unfortunately, use of the vinyl-element platforms described earlier (**1a**–**1d**) was not applicable in this synthesis. The synthesis starts with a novel Cu-catalyzed carbomagnesation across **19**, which proceeds with high regioselectivities and stereoselectivities. It was found that Cu-catalyzed addition did not occur at all with the corresponding 3-pyridyl-, 4-pyridyl-, and phenylsilanes, which clearly implicates the strong directing effect (CIPE) of the 2-pyridyl group on silicon. The sequential arylations at the C–Mg and C–Si (C–B) bonds of the resultant pyridylsilyl-substituted alkenylmagnesium compound **20** utilizing Pd-catalyzed cross-coupling reactions with aryl halides afforded the targeted tamoxifen-type tetrasubstituted olefins **22**.

By following the synthetic scheme described in Fig. 31, a wide array of electronically and structurally diverse tetrasubstituted olefins **22** can be prepared in a regio-controlled, stereo-controlled, and diversity-oriented manner. Representative products prepared are shown in Fig. 31.[46] Noteworthy features are that (i) the three aryl groups, which are believed to be important (essential) for anti-estrogenic activity,[45] can be varied at will because they all stem from readily available aryl iodides, and (ii) any isomer can be prepared by simply changing the order of application of the aryl iodides in the sequence.

7. Platform Synthesis of CDP840

During these investigations toward the development of multisubstituted olefin synthesis, we realized that these olefins

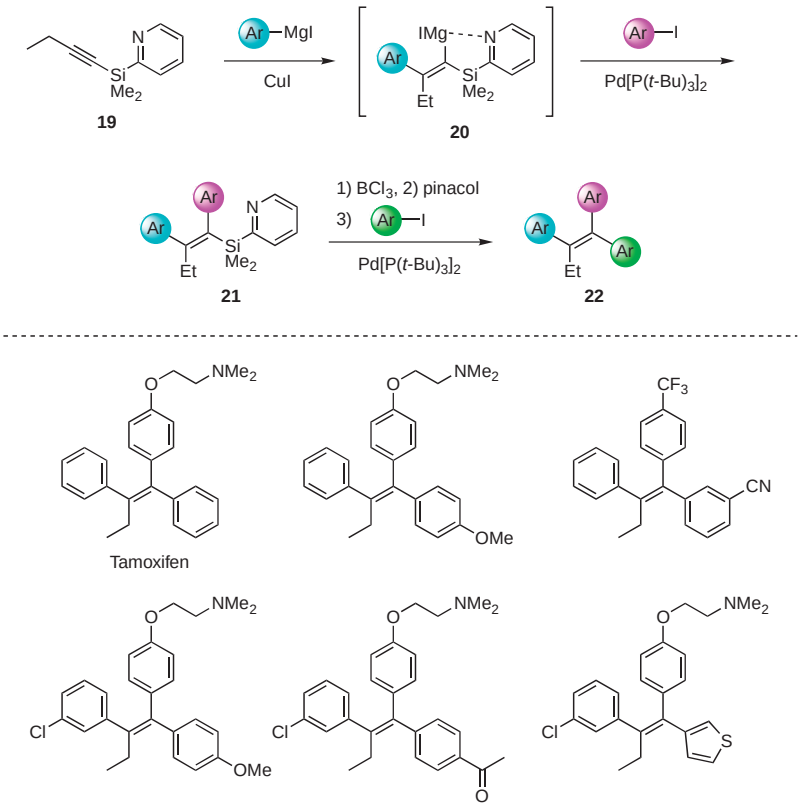

Fig. 31. Platform synthesis of tamoxifen-type tetrasubstituted olefins **22** using **19** as a platform.

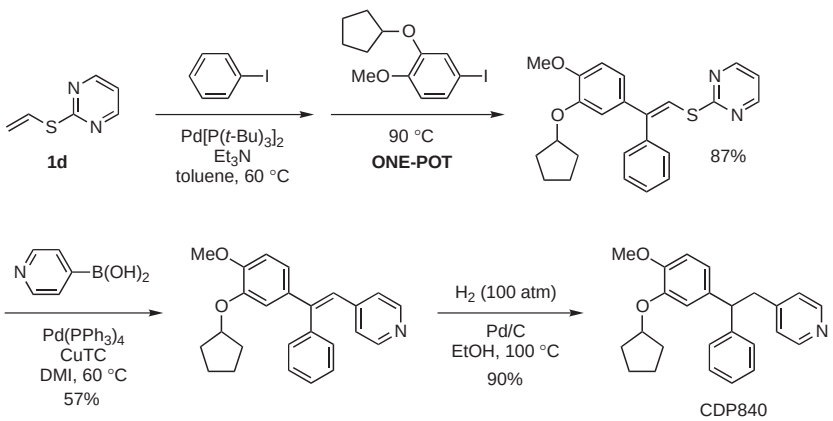

Fig. 32. Platform synthesis of CDP840 using **1d** as a platform.

could also be excellent precursors for densely substituted organic structures by functionalizing the remaining C=C core of multisubstituted olefins. During our investigations along this line, we developed a platform synthesis of pharmaceutically important 1,1,2-triarylethanes using **1d** as a platform.[47] This method includes a stereoselective double Mizoroki–Heck-type arylation, Liebeskind–Srogl-type cross-coupling reaction,[48] and Pd/C-catalyzed hydrogenation. A rapid synthesis of CDP840, a potential therapeutic agent for asthma as a selective phosphodiesterase (PDE) IV inhibitor,[49] has been established using this method (Fig. 32).[47]

Conclusion

The concept of platform synthesis has been successfully demonstrated as a useful strategy for making multisubstituted olefins in a programmable and diversity-oriented format. This simple yet powerful synthetic strategy allowed us not only to prepare multisubstituted olefin frameworks useful in pharmaceuticals such as tamoxifen, but also to construct previously unexplored functional C=C-based extended π-systems. Moreover, the programmable and diversity-oriented nature of our synthesis allowed us also to systematically construct chemical libraries of multisubstituted olefins very easily and rapidly, which has led to the discovery of a number of interesting fluorescent materials and properties.

Has our platform synthesis then entered the realm of a truly general synthesis of multisubstituted olefins? Unfortunately, the answer is still “no” at present. Our strategy permits a pro-

grammable synthesis of all possible isomers of trisubstitued and tetrasubstituted olefins, which had not been achieved previously. However, the introducible substituents are in many cases still limited to aryl, heteroaryl, and alkenyl groups in our platform synthesis. Clearly, more extensive investigations are needed to broaden the scope of introducible groups. If we can overcome these limitations, we may be close to a truly general olefin synthesis.

During this research program, we have extensively focused on multisubstituted olefins motivated by synthetic challenge as well as potential applications in materials science and pharmaceutical science. However, we feel that our concept of platform synthesis should also have broad applicability in the generation of other previously unexplored multifunctional molecules.[50] The library-based approach using platform synthesis should find many uses in the development and understanding of materials science and life science.

We would like to express our sincere appreciation to all the co-workers, whose names are cited in the references, for their invaluable contributions. This work was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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50 For applications of platform synthesis to the construction of pyrimidine-core extended π-systems, see Ref. 31.

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