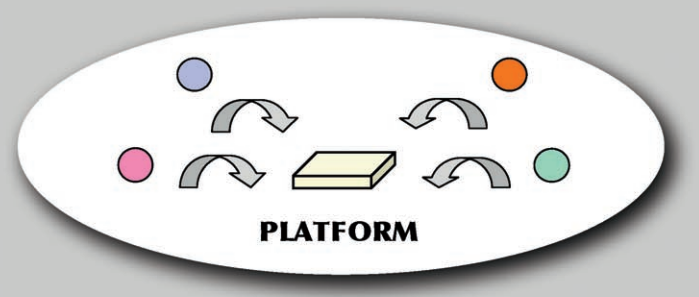
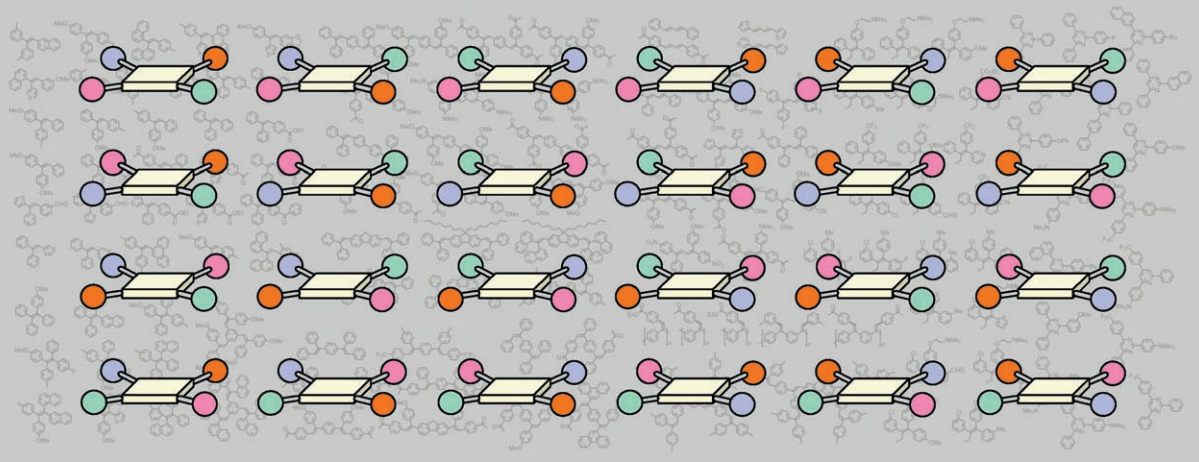
PLATFORM SYNTHESIS

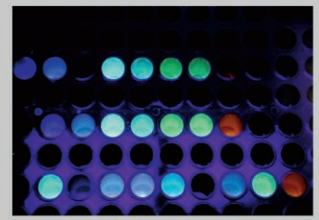
Programmable assembly of components onto a platform



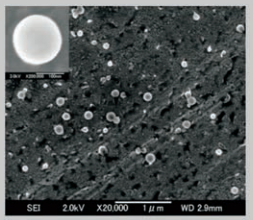
Rapid and systematic generation of molecular diversity



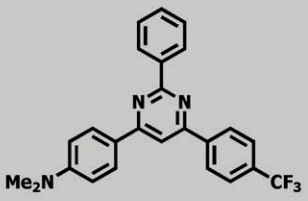
Application to materials science and medicinal chemistry



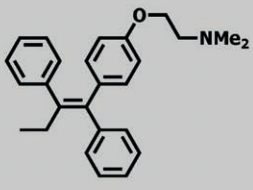
Fluorescent Library



Fluorescent Nanoparticles



Solvatofluoro-chromic Materials



Anti-Breast Cancer Drug

... and more

DOI: 10.1002/chem.200500958

Platform Synthesis: A Useful Strategy for Rapid and Systematic Generation of Molecular Diversity

Kenichiro Itami*[a] and Jun-ichi Yoshida*[b]

Abstract: Emergence of library-based approaches have changed the way of developing new functional molecules in materials science and pharmaceutical science. Therefore, reliable methods for rapid and systematic generation of functional molecules are highly called for in this field. We herein describe our concept of "platform synthesis" as a useful strategy for generating molecular diversity. This simple yet powerful strategy realizes the synthesis of a number of interesting multifunctional molecules, such as 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.

Keywords: combinatorial chemistry · materials science · medicinal chemistry · platform synthesis · synthetic methods

Introduction

Generation of new functional materials (molecules) is a key in the progress of science. Through providing efficient methods and strategies for making useful organic frameworks, synthetic organic chemistry has contributed to the development and understanding of materials science and life science in many ways. Although a target-oriented synthesis of complex natural products and a rational design of functional materials has been a main stream in organic synthesis, the emergence of combinatorial chemistry[1] and diversity-oriented synthesis[2] has changed the way of planning and doing chemical synthesis as a whole. Because elucidation of structure–activity (structure–property) relationships is not necessarily easy and, hence, a rational design of molecules is often difficult in medicinal chemistry and materials science, such library-based approaches enable rapid identification and optimization of functional materials in many cases.[1] In addition, there is a high probability to discover unexpected functions with these library-based approaches. Therefore, reliable strategies and methodologies for generating molecular diversity are highly called for in this field. This article describes our concept of "platform synthesis" and its application to the synthesis of various functional materials.

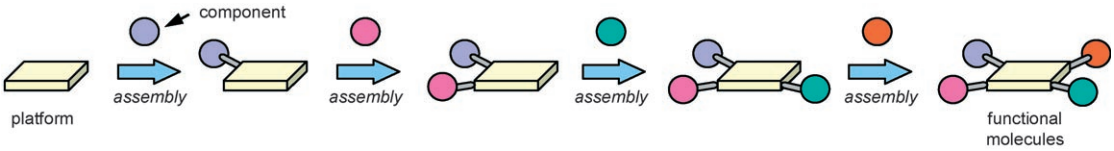
[a] Prof. K. Itami
Research Center for Materials Science
Nagoya University, Nagoya 464–8602 (Japan)
Fax: (+81) 52-788-6098
E-mail: itami@chem.nagoya-u.ac.jp

[b] Prof. J. Yoshida
Department of Synthetic Chemistry and Biological Chemistry
Graduate School of Engineering, Kyoto University
Kyoto 615–8510 (Japan)
Fax: (+81) 75-383-2727
E-mail: yoshida@sbchem.kyoto-u.ac.jp

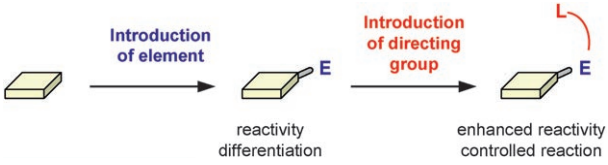
Platform Synthesis

The orthogonal and sequential functionalization[1d] of a simple molecule bearing multiple reaction sites (platform) serve as a powerful synthetic strategy that should provide enormous opportunity for diversity-oriented synthesis as well as target-oriented synthesis (Scheme 1). To effectively accomplish such platform syntheses, it is necessary that reactivities of those reaction sites be substantially differentiated. To realize such differentiation, those reaction sites should be stable unless activated by promoter or catalyst. It is also important to note that reactivities should be sufficiently high even after introduction of sterically demanding substituents.

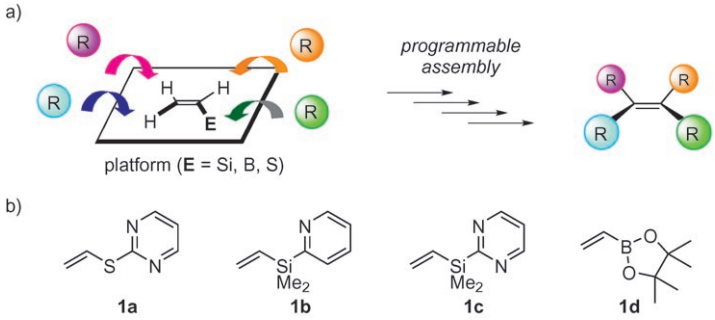
Our approach for such platform synthesis has been to utilize organoelement compounds, such as organosilicon, -sulfur, and -boron compounds, as platforms (Scheme 2). The strong stereo-electronic bias exerted by a suitably positioned element (E), would allow reactivity differentiation of potential reaction sites, thereby site-selective installation of



Scheme 1. Schematic representation of platform synthesis.



Scheme 2. Organoelement compound having directing group as a platform.



Scheme 3. a) Platform synthesis of multisubstituted olefins. b) Vinyl–element platforms developed so far.

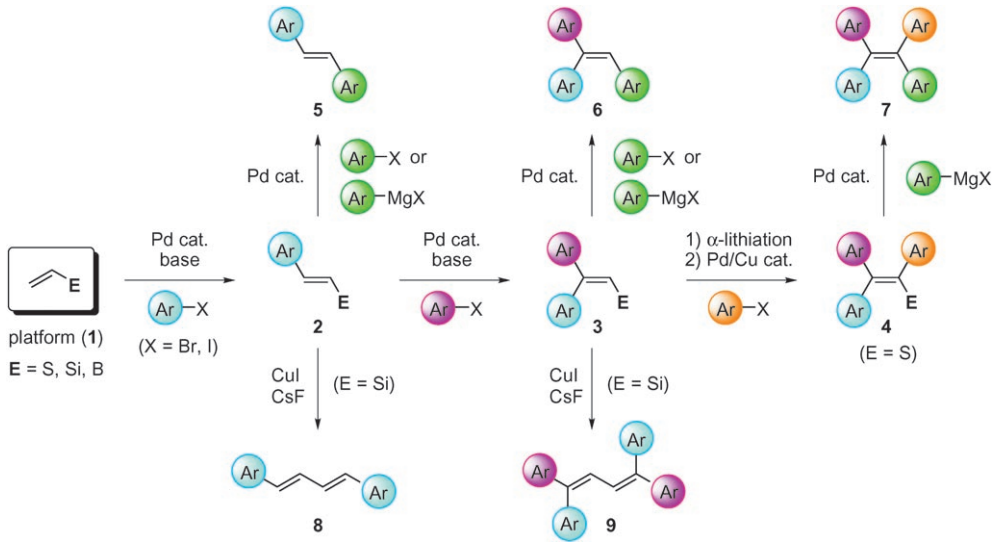
substituents onto a platform. In addition to this simple concept, we often utilize catalyst- or reagent-directing groups, such as pyridyl group, on the element.[3,4] The presence of these groups permits a number of metal-mediated component-assembling reactions that are essentially unattainable without such groups by virtue of effective coordination of the directing group to metals. It is also noteworthy that some directing groups such as pyridyl group also function as phase tags for separation.[5] Nowadays, automated synthesis is a powerful tool for the construction of large chemical libraries, but separation of products is often a bottleneck of solution-phase synthesis. The phase-tag approach provides a solution to this problem.[6] Thus, our approach of platform synthesis involves an orchestrated interplay of organoelement chemistry and coordination chemistry.

Platform Synthesis of Multisubstituted Olefins

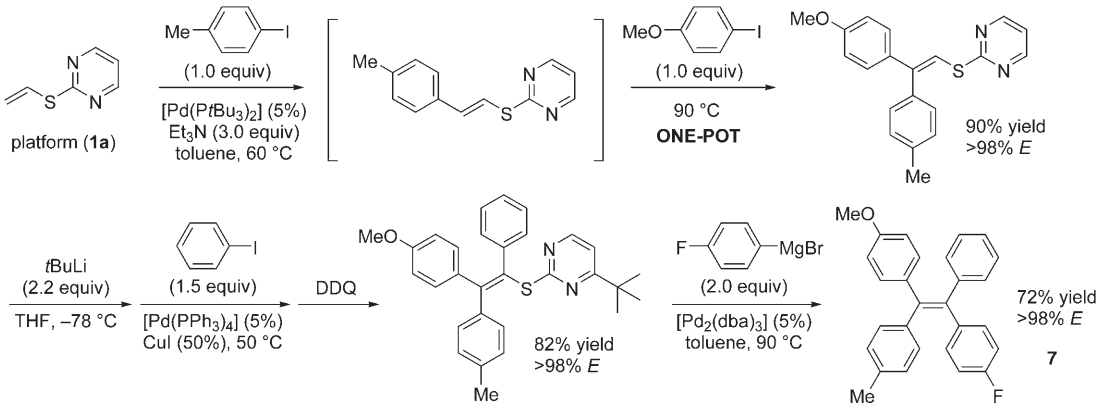
The regio- and stereoselective synthesis of multisubstituted olefins is one of the most challenging subjects in organic synthesis. In view of synthetic challenge as well as potential applications as functional materials and pharmaceuticals, we have initiated a program directed toward the development of a programmable and diversity-oriented synthesis of multisubstituted olefins.[7] We envisaged that the sequential assembly (installations) of substituents onto a C=C core of an ethylene derivative substituted by a suitable element (E) should be a straightforward strategy for multisubstituted olefin synthesis (Scheme 3a). 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 nonequivalent, thereby distinguishable in principle in component-assembling reactions. This strategy differs from the classical olefin synthesis as exemplified by Wittig reaction and its analogues that connect two components with the creation of a C=C bond, whereby the selectivity (stereoselectivity) would be inevitably dependent on the existing substituents.[8] Although conceptually intriguing, such an approach has been rather unexplored because of the apparent difficulty in controlling the reactivity at the desired bonds.

We developed several vinyl–element compounds **1** (CH_2=CH–E) that function as useful platforms (Scheme 3b); vinyl sulfide (**1a**),[9] vinylsilanes (**1b** and **1c**),[10–14] and vinyl boronate ester (**1d**).[15,16] The basic transformations based on **1** are shown in Scheme 4. In the presence of a Pd catalyst and base, these vinyl–element compounds **1** undergo arylation (Mizoroki–Heck type reaction; MHR)[17] with aryl halides at the β-C–H bond (**1**→**2**). Essentially no arylation takes place in the absence of catalyst-directing groups such as a pyridyl group on **1**, attesting to the strong directing effect of these groups.[18] The suitably positioned nitrogen atoms of pyridyl and pyrimidyl group might accelerate the rate-determining C=C π complexation and successive carbopalladation (insertion) events in MHR.[10] The occurrence of pyridyl-to-palladium coordination was demonstrated by ^{1}H NMR spectroscopy and X-ray crystal structure analysis of some key palladium complexes.[12] Moreover, because of the strong directing effect, a hard-to-achieve double MHR[19] is accomplished (**1**→**2**→**3**), which allows us to install two aryl groups at the two β-C–H bonds in one-pot.[12] The stereoselectivities of this double MHR are usually very high (>95%).

The successive installation of an aryl group at the α-C–H bond can be achieved by the α-lithiation[20] of **3** with *t*BuLi and a subsequent cross-coupling reaction (CCR)[21] with an aryl halide in the presence of [$Pd(PPh_3)_4$]/CuI catalyst.[9] This procedure provides **4** in high yields with virtually complete retention of stereochemistry, although it works well only for the vinyl sulfide platform **1a** at present. The final CCR of those alkenyl–element compounds (**2**–**4**) results in the production of multisubstituted ethenes (**5**–**7**). We also developed an efficient method for the homo-coupling reaction of alkenylsilanes (**2** and **3**) using CuI and CsF as pro-



Scheme 4. General synthetic scheme for multisubstituted olefins using **1** as a platform.

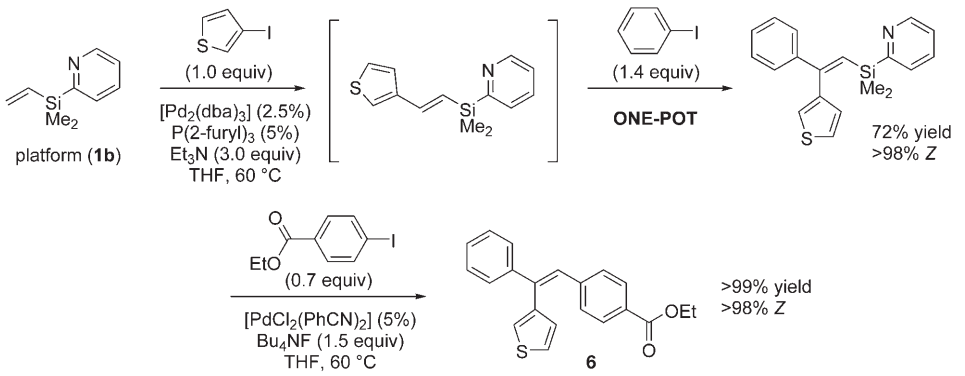


Scheme 5. Representative synthesis of tetraarylethene **7** using **1a** as a platform.

moters for the synthesis of multisubstituted butadienes.[13] With this method in hand, 1,3-butadienes with two or four electronically varied aryl groups (**8** and **9**) can be prepared very efficiently. Representative syntheses of tetraarylethene **7** (using **1a**)[9] and triarylethene **6** (using **1b**)[12] are shown in Schemes 5 and 6, respectively.

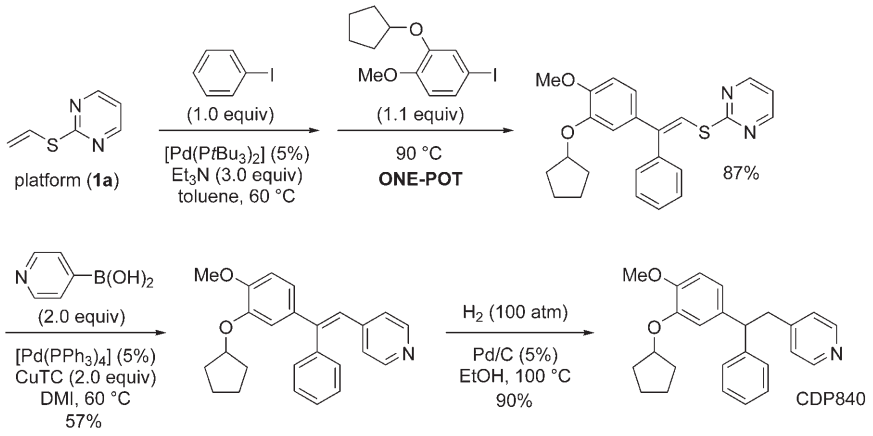
Noteworthy features of present method are that 1) all aryl groups assembled stem from readily available aryl halides or their Grignard reagents, 2) the installation of aryl groups at the desired position can be achieved by the appropriate order of addition, and 3) simple alteration of addition order of aryl halides in the sequence results in the production of all possible isomers of multisubstituted olefins.

Based on a similar approach, we recently developed a platform synthesis of 1,1,2-triarylethanes using **1a** as a platform.[22] This method includes a stereoselective double Mizoroki–Heck type arylation, Liebeskind–Srogl type cross-coupling reaction,[23] and Pd/C-catalyzed hydrogenation. A

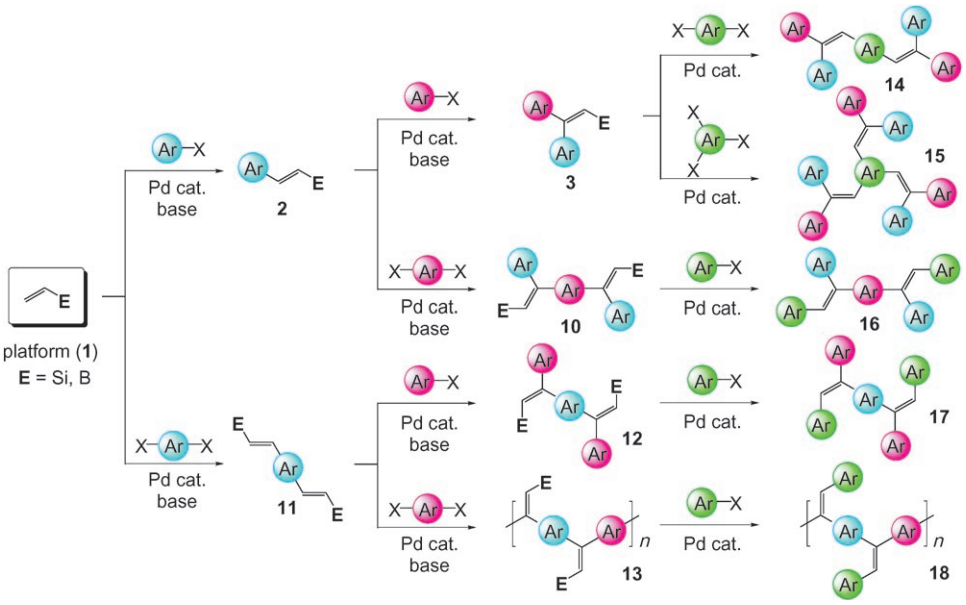


Scheme 6. Representative synthesis of triarylethene **6** using **1b** as a platform.

rapid synthesis of CDP840, a potential therapeutic agent for asthma as a selective phosphodiesterase (PDE) IV inhibitor,[24] has been established by using this method (Scheme 7).[22]



Scheme 7. Platform synthesis of CDP840.



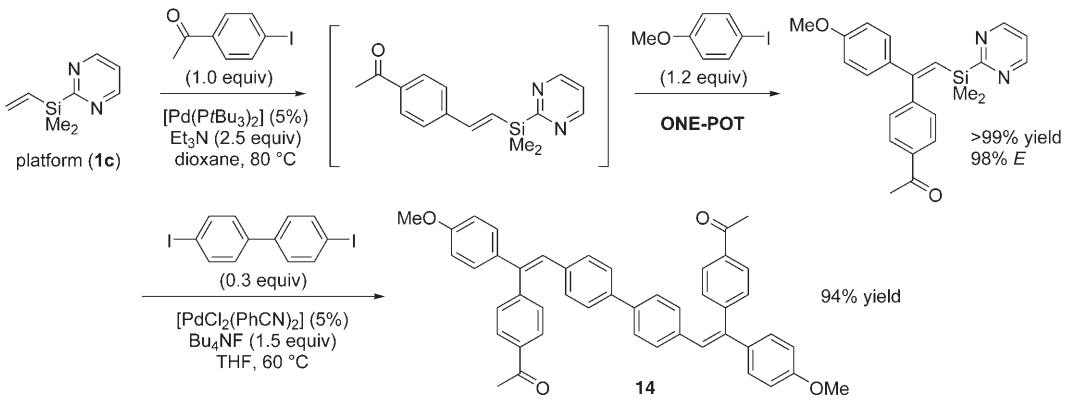
Scheme 8. Systematic construction of arylethene-based extended π systems **14**–**18**.

Rapid and Systematic Construction of Arylethene-Based Extended π Systems

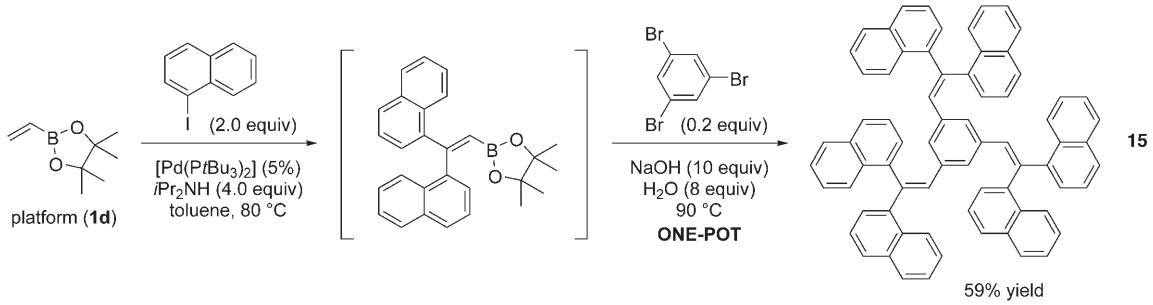
The above-mentioned platform synthesis of multisubstituted olefins represents a new strategy that permits assembly of π systems, such as aryl groups, onto a C=C core (minimal π unit) in a programmable and diversity-oriented format. Because π-assembling sites are programmed in our synthesis, the strategic 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 Scheme 4 results in the selective and systematic production of various types of arylethene-based extended π systems, which are otherwise difficult to construct (Scheme 8).[14,15] As platforms for this study, we used vinylsilanes (**1b** and **1c**) and vinyl boronate **1d**.

For example, the treatment of **3** (double-MHR product of **1**) with aryl dihalides ArX_2 under the influence of Pd catalyst results in the production of the interesting extended π system **14**. The use of trifunctional π systems is also interesting. For example, when aryl trihalides (ArX_3) are used in the final CCR with **3**, a starburst π system **15** can be prepared with ease. When the double-MHR/CCR sequence is performed by using the addition order ArX/ArX_2/ArX and ArX_2/ArX/ArX, extended π systems with interesting structures (**16** and **17**) are selectively produced. Moreover, when a double MHR is performed with ArX_2 alone, an unprecedented type of polymerization takes place. The successive CCR 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 (MHR and CCR), and common reagents (aryl halides). Representative syntheses of **14** (using **1c**)[14] and **15** (using **1d**)[15] are shown in Schemes 9 and 10, respectively.

By following these synthetic schemes described in Schemes 4 and 8, we succeeded in rapidly making chemical libraries of arylethene-based extended π systems (more than 150 compounds), from which highly fluorescent organic materials with a wide range of color variations (blue–red) were found (Figure 1).[13–15] The measurement of photophysical properties showed that the fluorescence quantum yields as well as emission color depend significantly on the attaching sites and the nature of the aryl groups attached. In addition, we found that the fluorescence efficiency of these extended π systems generally and dramatically increases in the solid (aggregation) state.[14,25] Moreover, we found that such an aggregation-induced en-



Scheme 9. Representative synthesis of **14** using **1c** as a platform.



Scheme 10. Representative synthesis of **15** using **1d** as a platform.

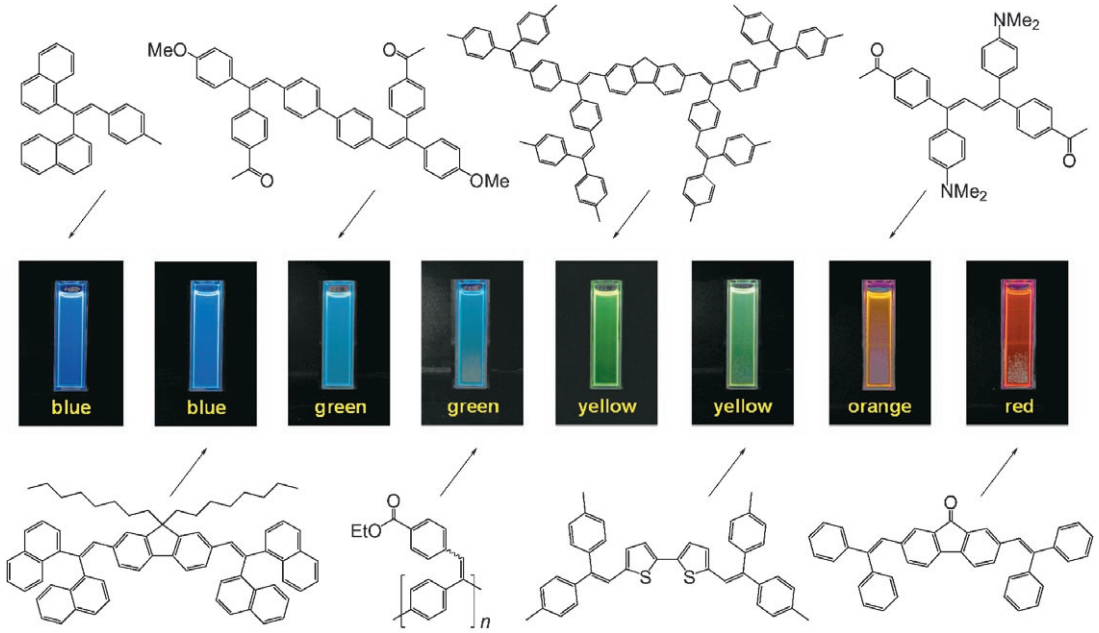


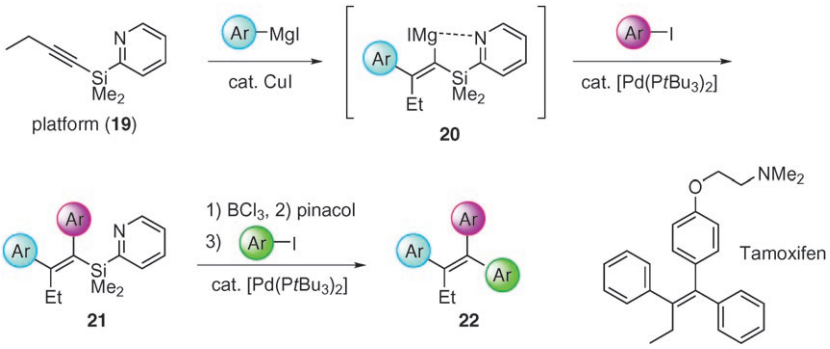
Figure 1. Representative fluorescent molecules found in our library.

hanced emission can be also observed in dioxane/water mixtures with high water contents, in which the formation of molecular aggregates such as nanoparticles has been indicated.[14] In addition to the increased chance of discovering new materials, the increased chance of discovering such interesting photophysical properties is clearly the advantage of diversity-oriented synthesis in fluorescent materials science, whereby the properties are often not predictable.

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, which is the most important anti-breast-cancer drug in clinical use and has the potential to be used as a chemopreventive breast-cancer agent.[26]

We have developed a general synthetic scheme for tamoxifen-type tetrasubstituted olefins using alkynyl(2-pyridyl)silane **19** as a platform (Scheme 11).[27,28] Unfortunately, use



Scheme 11. Platform synthesis of tamoxifen-type tetrasubstituted olefins.

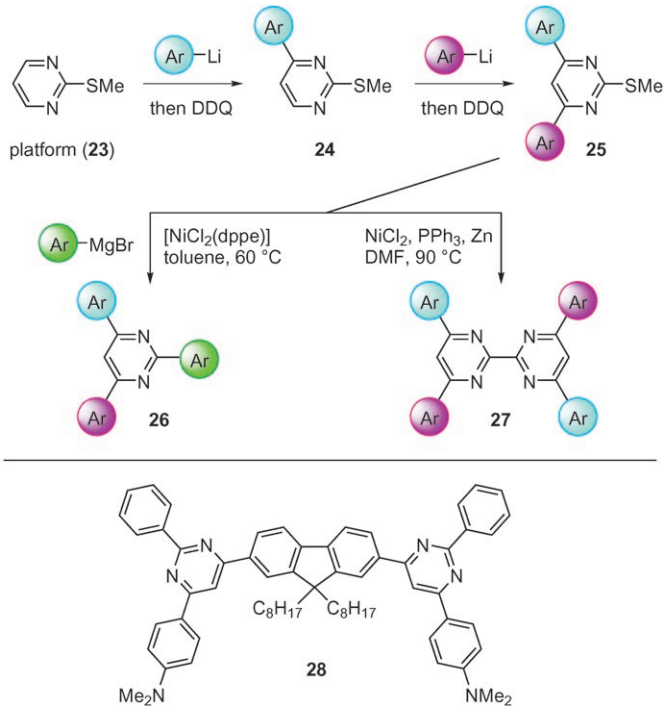
of the vinyl–element platforms described earlier (**1a–d**) was not applicable in this synthesis. The synthesis starts with a novel Cu-catalyzed carbomagnesation across **19**, which proceeds with high regio- and stereoselectivities. It was found that Cu-catalyzed addition did not occur at all with the corresponding 3-pyridyl, 4-pyridyl, and phenylsilanes, which clearly implicates the strong directing effect (complex-induced proximity effect) of the 2-pyridyl group on silicon.[29] 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 Scheme 11, a wide array of electronically and structurally diverse tetrasubstituted olefins (**22**) can be prepared in a regio-controlled, stereo-controlled, and diversity-oriented manner. Noteworthy features are that 1) the three aryl groups, which are believed to be important (essential) for anti-estrogenic activity,[26] can be varied at will, because they all stem from readily available aryl iodides; and 2) any stereo- and regioisomer can be prepared by simply changing the order of application of the aryl iodides in the sequence.

Platform Synthesis of Pyrimidine-Core Extended π Systems

Having substantiated the potential of platform synthesis as a useful strategy for generating molecular diversity, we next became interested in the development of such a synthesis for heteroaryl-core extended π systems, because it is well known that the introduction of a heteroaryl moiety into extended π systems often brings about a number of interesting properties that are useful in the development of advanced electronic and photonic materials.[30] Fortunately, our investigations along this line resulted in the accomplishment of sequential assembly of π systems onto the pyrimidine core (platform) as a useful method for the construction of pyrimidine-core extended π systems.[31]

We demonstrated the usefulness of 2-methylthiopyrimidine (**23**) as a platform in this strategy, and the representative π-assembling reactions are shown in Scheme 12. The nucleophilic addition of ArLi to **23**, followed by DDQ oxidation resulted in the production of **24**.[32] The iterative reaction sequence then gave **25**. The resulting adduct was further allowed to react with ArMgBr under the catalytic influence of $[NiCl_2(dppe)]$ to afford 2,4,6-triarylpyrimidines **26**.[33] Furthermore, the treatment of **25** with $NiCl_2/PPh_3/Zn$ in DMF resulted in a novel C–S homocoupling reaction giving substituted 2,2′-bipyrimidines **27**. By applying dilithium reagents ($ArLi_2$) in place of ArLi in the first and/or second π-assembling reactions, interesting extended π systems, such as **28** can also be prepared very efficiently.



Scheme 12. Platform synthesis of pyrimidine-core extended π systems.

By following this synthetic scheme, interesting pyrimidine-core π systems were rapidly constructed in a programmable fashion. Fortunately we were able to find some novel functional materials from a relatively small library (ca. 50 compounds) of multisubstituted pyrimidines. For example, 2,4,6-triarylpyrimidines with an electron-releasing *p*-$Me_2NC_6H_4$ group and electron-accepting *p*-$CF_3C_6H_4$ group attached, such as **29**, exhibit strong positive solvatofluorochromism.[31] The emissive behaviors of **29** with various solvents are shown in Figure 2. The decrease in the fluorescence energy with increasing solvent polarity corresponds to an increase in the dipole moment, indicating the charge-transfer character of the emitting state. Nevertheless, the realization of a wide range of wavelengths with reasonable fluorescence efficiency is notable. Its application as a fluorescent probe might be interesting.

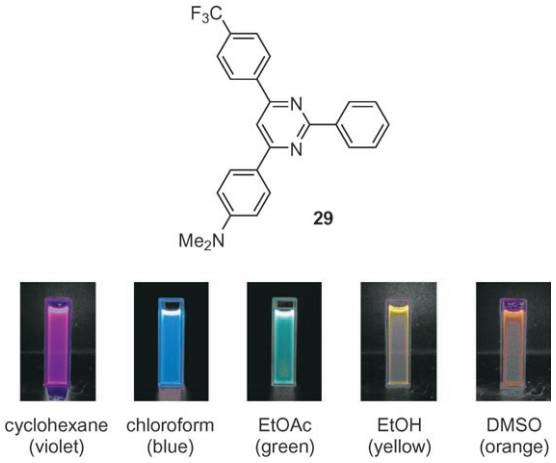


Figure 2. Emmisive behaviors of **29** with various solvents.

Summary and Outlook

Our approach of platform synthesis has been successfully demonstrated as a useful strategy for generating molecular diversity. This simple yet powerful strategy realizes the synthesis of interesting multifunctional molecules, such as multisubstituted olefins, in a programmable and diversity-oriented format. The successful discovery of a number of interesting materials (e.g., highly fluorescent molecules, fluorescent cross-conjugated polymers, fluorescent nanoparticles, and solvatofluorochromic materials) and properties (e.g., aggregation-induced enhanced emission) speaks well for the potential of the platform strategy in the development of functional materials. The successful syntheses of pharmaceutically important molecules, such as tamoxifen and CDP840, demonstrate the importance of the present strategy in medicinal chemistry. Although most of the platform syntheses described herein are based on the interplay of organoelement chemistry and coordination chemistry (directed reactions), the concept itself should not be limited to this kind. The evolution of other platforms will inspire novel applications (such as chemical genetics) and hopefully enable the construction of as-yet unexplored chemical libraries to face more challenging quest in science.

Acknowledgements

We thank all the collaborators who contributed to the results reported in this article. This work was supported in part by Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan. K.I. is grateful to Mitsui Chemicals for the Catalysis Science Award of Encouragement.

[1] a) *Molecular Diversity and Combinatorial Chemistry Libraries and Drug Discovery*, American Chemical Society, **1996**; b) *Combinatorial Chemistry—Synthesis and Applications* (Eds.: S. R. Wilson, A. W. Czarnik), Wiley, New York, **1997**; c) H. An, P. D. Cook, *Chem. Rev.* **2000**, *100*, 3311; d) D. L. Boger, J. Desharnais, K. Capps, *Angew. Chem.* **2003**, *115*, 4270; *Angew. Chem. Int. Ed.* **2003**, *42*, 4138; e) B. Jandeleit, D. J. Schaefer, T. S. Powers, H. W. Turner, W. H. Weinberg, *Angew. Chem.* **1999**, *111*, 2648; *Angew. Chem. Int. Ed.* **1999**, *38*, 2494.
[2] a) S. L. Schreiber, *Science* **2000**, *287*, 1964; b) M. J. Valler, D. Green, *Drug Discovery Today* **2000**, *5*, 286; c) P. Arya, D. T. H. Chou, M. G. Baek, *Angew. Chem.* **2001**, *113*, 351; *Angew. Chem. Int. Ed.* **2001**, *40*, 339; d) M. D. Burke, E. M. Berger, S. L. Schreiber, *Science* **2003**, *302*, 613; e) M. D. Burke, S. L. Schreiber, *Angew. Chem.* **2004**, *116*, 48; *Angew. Chem. Int. Ed.* **2004**, *43*, 46.
[3] For excellent reviews on directed chemical reactions, see: a) A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307; b) P. Beak, A. I. Meyers, *Acc. Chem. Res.* **1986**, *19*, 356; c) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879; d) P. Beak, A. Basu, D. J. Gallagher, Y. S. Park, S. Thayumanavan, *Acc. Chem. Res.* **1996**, *29*, 552; e) M. C. Whisler, S. MacNeil, V. Snieckus, P. Beak, *Angew. Chem.* **2004**, *116*, 2256; *Angew. Chem. Int. Ed.* **2004**, *43*, 2206.
[4] For our related works using removable directing groups, see: a) K. Itami, T. Koike, J. Yoshida, *J. Am. Chem. Soc.* **2001**, *123*, 6957; b) K. Itami, T. Kamei, J. Yoshida, *J. Am. Chem. Soc.* **2001**, *123*, 8773; c) K. Itami, K. Mitsudo, J. Yoshida, *Angew. Chem.* **2001**, *113*, 2399; *Angew. Chem. Int. Ed.* **2001**, *40*, 2337; d) K. Itami, K. Mitsudo, J. Yoshida, *Angew. Chem.* **2002**, *114*, 3631; *Angew. Chem. Int. Ed.* **2002**, *41*, 3481; e) K. Itami, M. Mineno, T. Kamei, J. Yoshida, *Org. Lett.* **2002**, *4*, 3635; f) K. Itami, K. Mitsudo, K. Fujita, Y. Ohashi, J. Yoshida, *J. Am. Chem. Soc.* **2004**, *126*, 11058.
[5] a) J. Yoshida, K. Itami, K. Mitsudo, S. Suga, *Tetrahedron Lett.* **1999**, *40*, 3403; b) J. Yoshida, K. Itami, *J. Synth. Org. Chem. Jpn.* **2001**, *59*, 1086.
[6] a) D. P. Curran, *Angew. Chem.* **1998**, *110*, 1230; *Angew. Chem. Int. Ed.* **1998**, *37*, 1174; b) J. Yoshida, K. Itami, *Chem. Rev.* **2002**, *102*, 3693.
[7] K. Itami, J. Yoshida, *Bull. Chem. Soc. Jpn.*, in press.
[8] a) L. Kürti, B. Czakó, *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier Academic Press, Amsterdam, **2005**; b) R. C. Larock, *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, New York, **1999**.
[9] K. Itami, M. Mineno, N. Muraoka, J. Yoshida, *J. Am. Chem. Soc.* **2004**, *126*, 11778.
[10] K. Itami, K. Mitsudo, T. Kamei, T. Koike, T. Nokami, J. Yoshida, *J. Am. Chem. Soc.* **2000**, *122*, 12013.
[11] K. Itami, T. Nokami, J. Yoshida, *J. Am. Chem. Soc.* **2001**, *123*, 5600.
[12] K. Itami, T. Nokami, Y. Ishimura, K. Mitsudo, T. Kamei, J. Yoshida, *J. Am. Chem. Soc.* **2001**, *123*, 11577.
[13] K. Itami, Y. Ushiogi, T. Nokami, Y. Ohashi, J. Yoshida, *Org. Lett.* **2004**, *6*, 3695.
[14] K. Itami, Y. Ohashi, J. Yoshida, *J. Org. Chem.* **2005**, *70*, 2778.
[15] K. Itami, K. Tonogaki, Y. Ohashi, J. Yoshida, *Org. Lett.* **2004**, *6*, 4093.

[16] K. Tonogaki, K. Soga, K. Itami, J. Yoshida, *Synlett* **2005**, 1802.
[17] For a review on Mizoroki-Heck reaction, see: I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009.
[18] For a review on chelation-controlled Mizoroki-Heck reaction, see: M. Oestreich, *Eur. J. Org. Chem.* **2005**, 783.
[19] Multiple Mizoroki–Heck reactions: a) S. Bräse, A. de Meijere in *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E. Negishi), Wiley, New York, **2002**, p. 1179; b) P. Nilsson, M. Larhed, A. Hallberg, *J. Am. Chem. Soc.* **2001**, *123*, 8217.
[20] α-Lithiation of vinyl sulfides: K. Oshima, K. Shimoji, H. Takahashi, H. Yamamoto, H. Nozaki, *J. Am. Chem. Soc.* **1973**, *95*, 2694.
[21] For an excellent up-to-date treatment, see: *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed. (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**.
[22] N. Muraoka, M. Mineno, K. Itami, J. Yoshida, *J. Org. Chem.* **2005**, *70*, 6933.
[23] Liebeskind–Srogl type cross-coupling: a) C. Savarin, J. Srogl, L. S. Liebeskind, *Org. Lett.* **2001**, *3*, 91; b) L. S. Liebeskind, J. Srogl, *Org. Lett.* **2002**, *4*, 979; c) L. S. Liebeskind, J. Srogl, *J. Am. Chem. Soc.* **2000**, *122*, 11260.
[24] a) Celltech Therapeutics LTD, US Patent 5608070; b) Celltech Therapeutics LTD, US Patent 5622977; c) J. E. Lynch, W.-B. Choi, H. R. O. Churchill, R. P. Volante, R. A. Reamer, R. G. Ball, *J. Org. Chem.* **1997**, *62*, 9223; d) V, K. Aggarwal, I. Bae, H.-Y. Lee, J. Richardson, D. T. Williams, *Angew. Chem.* **2003**, *115*, 3396; *Angew. Chem. Int. Ed.* **2003**, *42*, 3274.
[25] For selected examples on aggregation-induced enhanced emission, see: a) R. Deans, J. Kim, M. R. Machacek, T. M. Swager, *J. Am. Chem. Soc.* **2000**, *122*, 8565; b) J. Luo, Z. Xie, J. W. Y. Lam, L. Cheng, H. Chen, C. Qiu, H. S. Kwok, X. Zhan, Y. Liu, D. Zhu, B. Z. Tang, *Chem. Commun.* **2001**, 1740; c) B.-K. An, S.-K. Kwon, S.-D. Jung, S. Y. Park, *J. Am. Chem. Soc.* **2002**, *124*, 14410.
[26] a) M. W. DeGregorio, V. J. Wiebe, *Tamoxifen and Breast Cancer*, 2nd ed., Yale University Press, New Haven, CT, **1999**; b) A. S. Levenson, V. C. Jordan, *Eur. J. Cancer* **1999**, *35*, 1628.
[27] K. Itami, T. Kamei, J. Yoshida, *J. Am. Chem. Soc.* **2003**, *125*, 14670.
[28] T. Kamei, K. Itami, J. Yoshida, *Adv. Synth. Catal.* **2004**, *346*, 1824.
[29] For a review on directed alkyne carbometalation, see: A. G. Fallis, P. Forgione, *Tetrahedron* **2001**, *57*, 5899.
[30] A. Kraft, A. C. Grimsdale, A. B. Holmes, *Angew. Chem.* **1998**, *110*, 416; *Angew. Chem. Int. Ed.* **1998**, *37*, 402.
[31] K. Itami, D. Yamazaki, J. Yoshida, *J. Am. Chem. Soc.* **2004**, *126*, 15396.
[32] For nucleophilic addition to pyrimidines, see: a) D. J. Brown in *The Pyrimidines*, Interscience, New York, **1994**; b) D. B. Harden, M. J. Mokrosz, L. Strekowski, *J. Org. Chem.* **1988**, *53*, 4137.
[33] For a review on Ni-catalyzed cross-coupling of sulfides, see: T. Y. Luh, Z. J. Ni, *Synthesis* **1990**, 89.

Published online: December 27, 2005

