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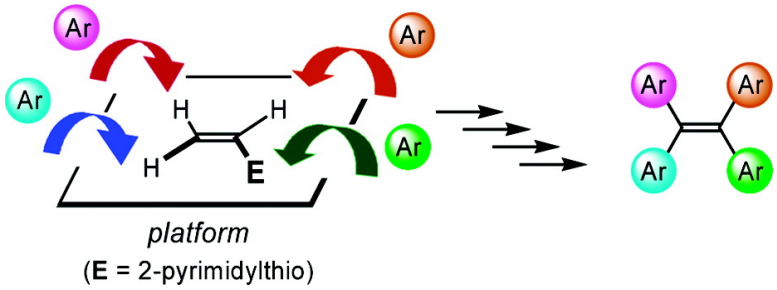

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Sequential Assembly Strategy for Tetrasubstituted Olefin Synthesis Using Vinyl 2-Pyrimidyl Sulfide as a Platform

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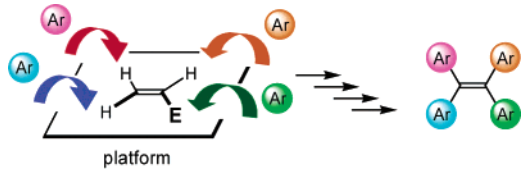
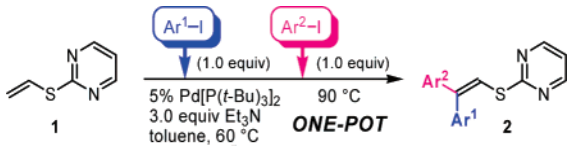
The regio- and stereoselective synthesis of multisubstituted olefins is one of the most challenging subjects in organic synthesis. In particular, the development of a general method for the synthesis of tetrasubstituted olefins with four different substituents has been a formidable challenge for chemists for years.[1] Moreover, in view of potential use as functional materials, an extended π-system based on tetrasubstituted olefin structure (tetraarylethenes) would be an interesting target.[2] We envisaged that the sequential assembly (installations) of π-components, such as aryl groups, onto a C=C core of an ethylene derivative substituted by a suitable heteroatom (E) would be a straightforward strategy for multisubstituted olefin synthesis. Because of the presence of such a heteroatom (E), the three C−H bonds (one α-C−H and two β-C−H bonds) and C−E bonds are nonequivalent, thereby distinguishable in principle toward π-component assembling reactions. This strategy differs from the classical olefin synthesis as exemplified by the Wittig reaction and its analogues that connect two components with the creation of a C=C bond, where the selectivity (stereoselectivity) would be dependent on existing substituent(s). As an assembling-site-controlling heteroatom (E), we paid particular attention to sulfur because of the rich chemistry of organosulfur compounds. We herein report a general method for the synthesis of tetrasubstituted olefins using vinyl 2-pyrimidyl sulfide (**1**) as a platform, realizing our concept.



As a π-component installation method at β-C−H bond of vinyl sulfide, we investigated the Pd-catalyzed Mizoroki−Heck reaction (MHR). Since there is only one example in the literature possibly reflecting the low reactivity of vinyl sulfide toward MHR,[3] we began by exploring a highly reactive vinyl sulfide as well as a catalyst. After extensive screening, we found that appending the catalyst-directing[4] 2-pyrimidyl group[5] on sulfur enormously enhances the reactivity of vinyl sulfide toward MHR. In addition, we found the Pd/P(*t*-Bu)$_3$ system[6] to be a highly active MHR catalyst in our synthesis. Moreover, because of the presence of catalyst-directing 2-pyrimidyl group on sulfur, hard-to-achieve double MHR[7] has been accomplished, which allows us to install two components at two β-C−H bonds in one pot.

The results of one-pot double MHR of vinyl 2-pyrimidyl sulfide (**1**) with aryl iodides are shown in Table 1. Various electronically and structurally diverse aryl iodides can be applied in this reaction to give β,β-diarylvinyl sulfides **2**. The yields are greater than 90% in many cases even using equimolar quantity of each reagent. Moreover, it is also possible to install different aryl groups

Table 1. One-Pot Double Mizoroki−Heck Reaction of **1** with Aryl Iodides



run	Ar^1	Ar^2	**2** (yield, %)
1[a]	phenyl (**a**)	phenyl (**a**)	**2aa** (93)
2[a]	2-methylphenyl (**b**)	2-methylphenyl (**b**)	**2bb** (90)
3[a]	3-methylphenyl (**c**)	3-methylphenyl (**c**)	**2cc** (81)
4[a]	4-methylphenyl (**d**)	4-methylphenyl (**d**)	**2dd** (91)
5[a]	4-methoxyphenyl (**e**)	4-methoxyphenyl (**e**)	**2ee** (92)
6[a]	1-naphthyl (**f**)	1-naphthyl (**f**)	**2ff** (95)
7	phenyl (**a**)	2-methylphenyl (**b**)	**2ab** (90)
8	phenyl (**a**)	4-methylphenyl (**d**)	**2ad** (88)
9	phenyl (**a**)	4-methoxyphenyl (**e**)	**2ae** (88)
10	4-methylphenyl (**d**)	phenyl (**a**)	**2da** (94)
11	4-methylphenyl (**d**)	4-methoxyphenyl (**e**)	**2de** (89)
12	4-methoxyphenyl (**e**)	phenyl (**a**)	**2ea** (86)
13	4-methoxyphenyl (**e**)	4-methylphenyl (**d**)	**2ed** (86)
14	4-methoxyphenyl (**e**)	1-naphthyl (**f**)	**2ef** (90)
15	3-thienyl (**g**)	4-methylphenyl (**d**)	**2gd** (89)
16	3-thienyl (**g**)	4-methoxyphenyl (**e**)	**2ge** (94)
17	3-thienyl (**g**)	1-naphthyl (**f**)	**2gf** (92)

[a] Reactions were performed at 80 °C with 2.0 equiv of aryl iodides.

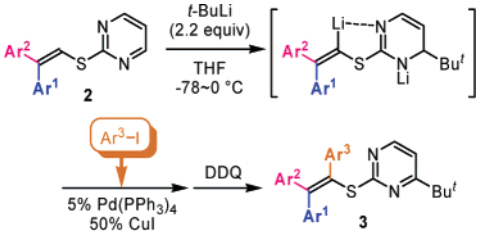
selectively onto **1** (runs 7−17). Thus, a toluene solution of **1** (1.0 equiv), Ar^1−I (1.0 equiv), Et$_3$N (3.0 equiv), and Pd[P(*t*-Bu)$_3$]$_2$ (5 mol %) was stirred at 60 °C for 3 h to afford monoarylated vinyl sulfide in situ. Thereafter, Ar^2−I (1.0 equiv) was added to the solution, and the mixture was stirred for an additional 15−24 h at 90 °C to give doubly arylated product **2**. The regio- and stereoselectivities of double MHR are greater than 95% as determined by NMR analysis.

Having established an efficient component assembling method at β-C−H bonds, we next embarked on the assembly of the third component at the α-C−H bond of **2**. After many experiments, we found that this could be achieved by the α-lithiation/cross-coupling sequence of **2** (Table 2). Thus, a THF solution of **2** was treated with *t*-BuLi (2.2 equiv) to afford α-lithiated species with *tert*-butyl group installed onto pyrimidine ring.[8] The use of an equimolar amount of *t*-BuLi only resulted in the alkylation onto pyrimidine ring. Since α-lithiation does not take place without the pyrimidyl group under otherwise identical conditions, we suppose that the 2-pyrimidyl group is also acting as a directing group in the α-lithiation of such sterically congested alkenyl sulfides.

The successive π-component assembling at α-position was accomplished by cross-coupling reaction (CCR) of the thus-obtained organolithiums with aryl halides under the influence of Pd(PPh$_3$)$_4$/CuI catalyst. The use of Cu cocatalyst is essential in this CCR. The treatment of the resultant crude solution with DDQ resulted in

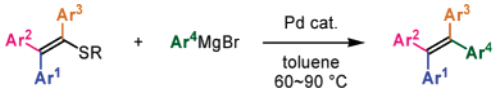
10.1021/ja045858t CCC: $27.50

Table 2. Synthesis of **3** through α-Lithiation/Cross-Coupling of **2**



run	**2**	Ar^3	**3** (yield, %)
1	**2aa**	4-methoxyphenyl (**e**)	**3aae** (82)
2	**2ae**	4-methylphenyl (**d**)	**3aed** (78)
3	**2de**	phenyl (**a**)	**3dea** (82)
4	**2ed**	phenyl (**a**)	**3eda** (70)
5	**2ed**	1-naphthyl (**f**)	**3edf** (65)
6	**2ff**	4-methylphenyl (**d**)	**3ffd** (55)

Table 3. Synthesis of Tetraarylethenes **4** and Triarylethenes **5**



3 (R = 2-(4-*tert*-butyl)pyrimidyl)
2 (Ar^3 = H, R = 2-pyrimidyl)

4
5 (Ar^3 = H)

run	sulfide	Ar^4	product (yield, %)
1[a]	**3aae**	phenyl (**a**)	**4aaea** (72)
2[a]	**3aae**	2-naphthyl (**h**)	**4aaeh** (46)
3[a]	**3aed**	4-methylphenyl (**d**)	**4aedd** (40)
4[a]	**3dea**	4-fluorophenyl (**i**)	**4deai** (52)
5[a]	**3eda**	4-fluorophenyl (**i**)	**4edai** (42)
6[a]	**3edf**	phenyl (**a**)	**4edfa** (22)
7[a]	**3edf**	2-naphthyl (**h**)	**4edfh** (14)
8[a]	**3edf**	2-thienyl (**j**)	**4edfj** (21)
9[a]	**3ffd**	phenyl (**a**)	**4ffda** (31)
10[b]	**2ab**	4-methoxyphenyl (**e**)	**5abe** (58)
11[b]	**2dd**	2-methylphenyl (**b**)	**5ddb** (62)
12[b]	**2cc**	2-naphthyl (**h**)	**5cch** (66)
13[b]	**2ee**	4-fluorophenyl (**i**)	**5eei** (85)
14[b]	**2ff**	4-methylphenyl (**d**)	**5ffd** (67)
15[b]	**2gd**	9-phenanthryl (**k**)	**5gdk** (63)
16[b]	**2ge**	3,4-(methylenedioxy)phenyl (**l**)	**5gel** (52)
17[b]	**2gf**	3-methoxyphenyl (**m**)	**5gfm** (58)
18[b]	**2ad**	4-methoxyphenyl (**e**)	**5ade** (76)
19[b]	**2ae**	4-methylphenyl (**d**)	**5aed** (69)
20[b]	**2da**	4-methoxyphenyl (**e**)	**5dae** (62)
21[b]	**2de**	phenyl (**a**)	**5dea** (73)
22[b]	**2ea**	4-methylphenyl (**d**)	**5ead** (76)
23[b]	**2ed**	phenyl (**a**)	**5eda** (81)

[a] Reaction conditions: **3**, Ar^4MgBr (3.0 equiv), $Pd_2(dba)_3$ (5 mol %), toluene, 90 °C, 20 h. [b] Reaction conditions: **2**, Ar^4MgBr (3.0 equiv), $Pd[P(t\text{-}Bu)_3]_2$ (5 mol %), toluene, 60 °C, 15 h.

the regeneration of the pyrimidine ring (oxidation) to finally provide α,β,β-triarylated vinyl sulfides **3** in good yields with virtually complete retention of stereochemistry.

As for the final π-component assembling method at the remaining C−S bond of α,β,β-triarylated vinyl sulfides **3**, we found that CCR with Grignard reagents (Ar^4MgBr)[9] under the influence of Pd catalyst is particularly effective. As listed in Table 3, a number of tetrasubstituted olefins **4** were prepared in moderate to good yields with virtually complete retention of stereochemistry (runs 1−9). When β,β-diarylated vinyl sulfides **2** were used as coupling partners, trisubstituted olefins **5** could also be prepared in a regio- and stereoselective fashion (runs 10−23).[10] In the triarylethene synthesis, we also demonstrated the preparation of all stereo- and regioisomers

Scheme 1

(**5ade**, **5aed**, **5dae**, **5dea**, **5ead**, and **5eda**) that are possible from a set of three aryl groups (**a**, **d**, and **e**) by changing the applying order of those aryl groups into the reaction sequence.

In summary, we have developed a programmable and diversity-oriented synthetic scheme for tetrasubstituted olefins through a site-selective and sequential assembly of π-components onto a C=C core of vinyl 2-pyrimidyl sulfide (Scheme 1). Noteworthy features are that (i) all components assembled stem from readily available organic halides or their Grignard reagents, (ii) the installation at the desired position can be achieved by the addition of the components in the appropriate order, and (iii) simple alteration of addition order in the sequence results in the production of all possible regio- and stereoisomers of multisubstituted olefins. As well as applications to pharmaceutical chemistry, we feel that the present strategy should find many uses for combinatorial lead-structure identification and optimization in the development of functional organic materials where the structure−property relationships are often not predictable. The investigations in this line as well as expanding the applicable components assembled are currently ongoing in our laboratory.

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Supporting Information Available: Experimental procedures and analytical and spectroscopic data of compounds (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Recent successful synthesis of tetrasubstituted olefins: (a) Zhou, C.; Emrich, D. E.; Larock, R. C. *Org. Lett.* **2003**, *5*, 1579. (b) Itami, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2003**, *125*, 14670.
(2) For a review on functional materials based on stilbenoid structures, see: Meier, H. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1399.
(3) Trost, B. M.; Tanigawa, Y. *J. Am. Chem. Soc.* **1979**, *101*, 4743.
(4) Directed Mizoroki−Heck reaction: (a) Bernocchi, E.; Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1992**, *33*, 3073. (b) Badone, D.; Guzzi, U. *Tetrahedron Lett.* **1993**, *34*, 3603. (c) Larhed, M.; Andersson, C. M.; Hallberg, A. *Tetrahedron* **1994**, *50*, 285. (d) Itami, K.; Nokami, T.; Ishimura, Y.; Mitsudo, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 11577. (e) Buezo, N. D.; de la Rosa, J. C.; Priego, J.; Alonso, I.; Carretero, J. C. *Chem.−Eur. J.* **2001**, *7*, 3890. (f) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2003**, *125*, 3430.
(5) The corresponding phenyl, 2-pyridyl, and pyrazyl analogues exhibited lower reactivity toward Mizoroki−Heck reactions.
(6) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989.
(7) (a) Bräse, S.; de Meijere, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002; p 1179. (b) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2001**, *123*, 8217. (c) Reference 4d.
(8) α-Lithiation of vinyl sulfides: Oshima, K.; Shimoji, K.; Takahashi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1973**, *95*, 2694.
(9) (a) Okamura, H.; Miura, M.; Takei, H. *Tetrahedron Lett.* **1979**, 43. (b) Wenkert, E.; Ferreira, T. W.; Michelotti, E. L. *J. Chem. Soc., Chem. Commun.* **1979**, 637. (c) Luh, T. Y.; Ni, Z. J. *Synthesis* **1990**, 89.
(10) The stereochemistry was determined by X-ray analysis of **5gel**.

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