Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 5569–5578

TETRAHEDRON

Diversification of shotgun process

Yoshifumi Nagano, Akihiro Orita and Junzo Otera*

Department of Applied Chemistry, Okayama University of Science, Ridai-cho, Okayama 700-0005, Japan

Received 1 May 2003; revised 14 May 2003; accepted 16 May 2003

Abstract—Three protocols for shotgun process are put forth in which simultaneous multi-fold reactions occur exclusively to each other. The first one involves simple combination of selective and non-selective reactions. Even if the simple protocol fails to give rise to the high selectivity, satisfactory outcome can be achieved by kinetic control or adjustment of functional groups.

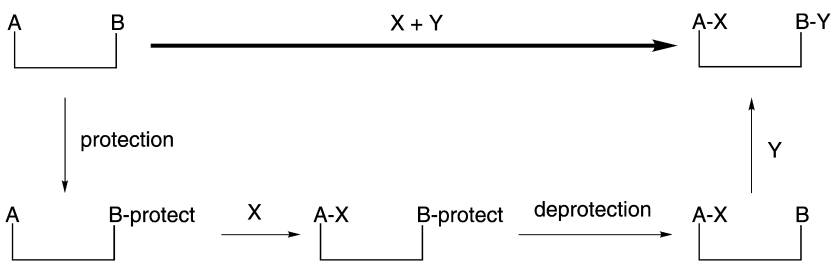
1. Introduction

Compaction of multi-step chemical processes is of great significance from a viewpoint of green chemistry. In this context, we put forth a new concept, 'shotgun process' where different reactions are feasible on the separate reaction sites without recourse to protection–deprotection procedures (Scheme 1).[1] The simplest protocol arises from the following case. Suppose that upon exposure to a mixture of reagents X and Y, A reacts with X exclusively while B exhibits no selectivity to react with both X and Y. Even under such circumstances, the desired one-pot exclusive reactions are achievable if the reaction between A and X is much faster than the reaction of B with X and Y. X is consumed totally by the former reaction before initiation of the reactions of B, which accordingly has no choice but to react with Y to results in exclusive formation of A–X and B–Y, respectively. However, such an ideal situation is often violated since the reagents are usually employed in excess to attain high conversions and, moreover, functional groups A and B are liable to experience interactions with each other or with X and Y at random even though the interactions are not strong enough to induce the reactions. As a result, the innate reactivity of the functional groups is altered. These interactions, however, do not necessarily cause deterioration of the selectivity but the improvement may be attained if appropriate conditions are fulfilled. We report herein that this is indeed the case and a variety of shotgun processes are feasible.[2]

2. Results and discussion

2.1. Simple shotgun process

An example of a typical shotgun process free from any of the complicated influences was offered as follows. Treatment of an equimolar mixture of benzylidene aniline (**1**) and naphthoquinone (**2**) with Danishefsky's diene **3** (1.2 equiv.) in the presence of $Yb(OTf)_3$ (20 mol%) led to exclusive reaction with **1** (Table 1, entry 1)[3] delivering a candidate for A–X formation in Scheme 1. On the other hand, a non-selective reaction took place with cyclopentadiene (**5**) (2.0 equiv.) under the same conditions to furnish products **6**[3] and **7**[4] derived from **1** and **2**, respectively (entry 2). Then, these two reactions were integrated into one pot, and only **4** and **7** were obtained quantitatively without contamination of **6** (entry 3). When the reaction of **1** with **3** (1.2 equiv.) was conducted in the presence of **5** (2.0 equiv.), **4** was obtained



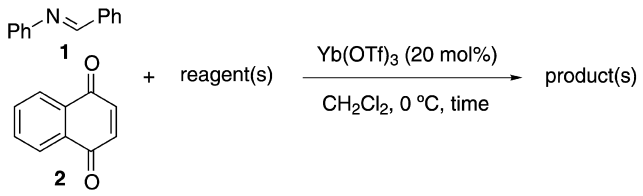
Scheme 1.

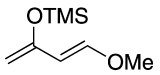
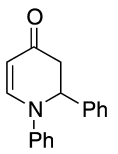
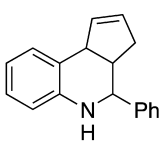
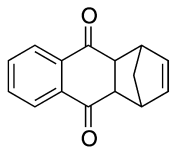
Keywords: shotgun process; allylation; Diels–Alder reaction; acetylation; scandium triflate; ytterbium triflate.

* Corresponding author. Tel.: +81-86-256-9525; fax: +81-86-256-4292; e-mail: otera@high.ous.ac.jp

0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00768-3

Table 1. Shotgun process consisting of two Diels–Alder reactions

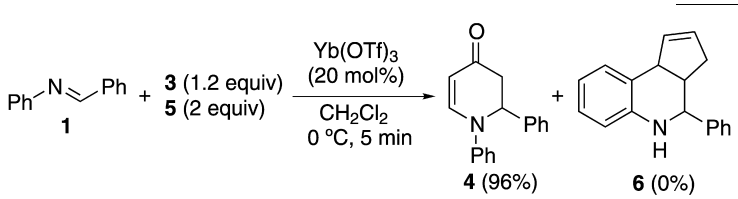


Entry	Reagent(s)	Time (h)	Product(s)[a]
1	 **3** (1.2 equiv)	6	 **4** (94%)
2	 **5** (2 equiv)	24	 **6** (5%)[b]  **7** (99%)
3	**3** (1.2 equiv.), **5** (2 equiv.)	24	**4** (92%), **7** (96%)

[a] Isolated yield after column chromatography.
[b] determined by GLC.

quantitatively after 5 min, no sign of formation of **6** being detected (Eq. (1)). Apparently, **1** reacted with **3** much faster than with **5** and the substrate had been used up before the latter reaction was initiated.

while tetraallytin (**9**) (0.3 mol equiv.) exhibited no selectivity towards both substrates to furnish **10**[5] and **11**[6] in 25 and 73% yields, respectively (entry 2). Treatment of these substrates and reagents in one shot again led to quantitative

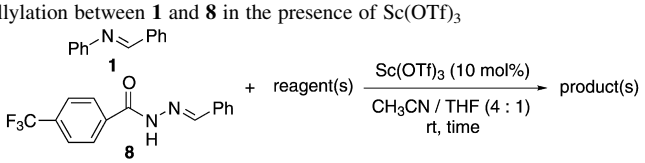


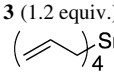
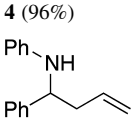
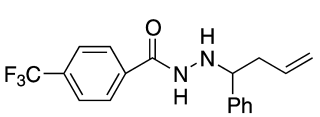
(1)

A similar simple shotgun process was observed with a combination between substrates **1/8** and reagents **3/9** (Table 2). Diels–Alder reaction between **1** and **3** took place quantitatively in the presence of $Sc(OTf)_3$ (entry 1)

formation of **4** and **11** as sole products (entry 3). An unambiguous evidence for the shotgun process was provided by quenching the reaction after 1 min (Eq. (2)). The reaction between **1** and **3** had finished already while

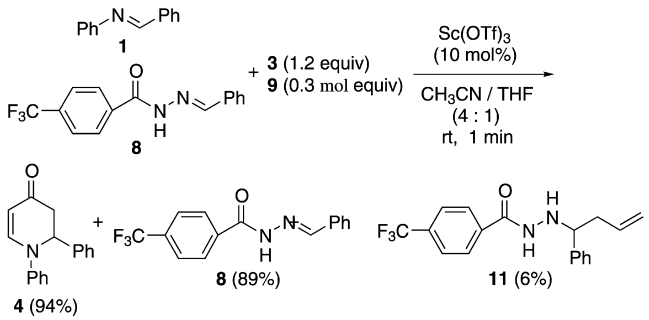
Table 2. Hetero-Diels–Alder reaction/allylation between **1** and **8** in the presence of $Sc(OTf)_3$



Entry	Reagent(s)	Time (h)	Producet(s)[a]
1	**3** (1.2 equiv.)	0.5	**4** (96%)
2	 **9** (0.3 mol equiv)	15	 **10** (25%)  **11** (73%)
3	**3** (1.2 equiv.), **9** (0.3 mol equiv.)	15	**4** (96%), **11** (95%)

[a] Isolated yield after column chromatography.

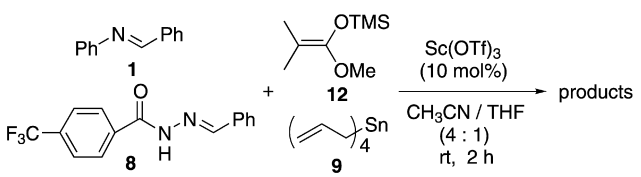
89% of **8** remained unreacted.



(2)

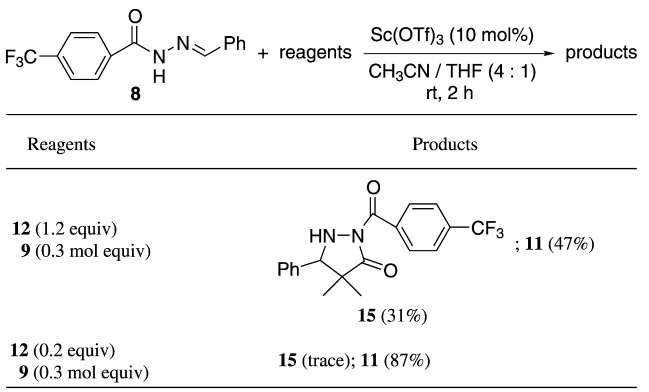
2.2. Kinetically controlled shotgun process

In striking contrast to **1**, ketene silyl acetal **12** responded to the same substrate mixture in a less selective manner. Thus, the reaction of **12** (1.2 equiv.) with a mixture of **1** and **8** (each 1 equiv.) furnished two products, **13**[7] and **14**[8] (Eq. (3)). Nevertheless, integration of this reaction with the allylation resulted in only two products **13** and **11** quantitatively (Eq. (4)). Apparently, both innately non-selective reactions were rendered completely selective. Similar improvement of the substrate selectivity is also achievable by another one-pot protocol, parallel recognition where both reactions proceed simultaneously in parallel.[9] However, it was suggested by quenching the reaction at an early stage that the shotgun process operated in the present case, after 1 min, **1** was totally consumed by reaction with **12** to give a 96% yield of **13** while only a 10% yield of **11** was obtained leaving a large amount of **8** intact (Eq. (5)). The selectivity is highly sensitive to the amount of the substrates, and the use of 1.2 equiv. of **12** and 0.3 mol equiv. of **9** is crucial for attaining the perfect selectivity (standard conditions). As shown in Scheme 2, employment of 1.1 equiv. of **12** allowed allylation of imine **1** slightly to give **10** in 2% yield while increase of the amount of **12** (1.5 equiv.) induced reaction of this reagent with hydrazone **8** to give **14** in 15% yield concomitant with a decreased yield of the allylation of **8**. The increase of **9** up to 0.5 mol equiv. triggered allylation of **1** (2% yield). Treatment of the mixture of **12** and **9** in the same ratio as the standard conditions with **1** afforded **13** exclusively (Eq. (6)). When the same mixture was exposed to **8**, both reagents reacted to give the corresponding products in comparable



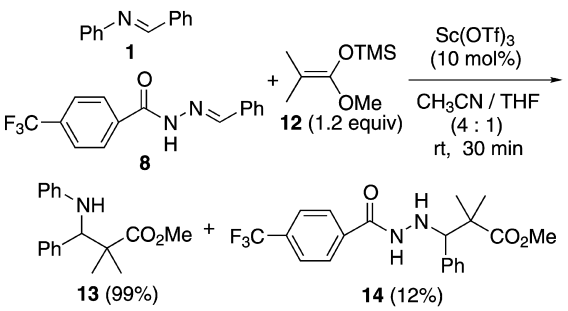
12 (equiv)	**9** (mol equiv)	Products
1.1	0.3	**13** (96%); **10** (2%); **11** (80%)
1.5	0.3	**13** (97%); **14** (15%); **11** (58%)
1.2	0.5	**13** (98%); **10** (2%); **11** (84%)

Scheme 2.

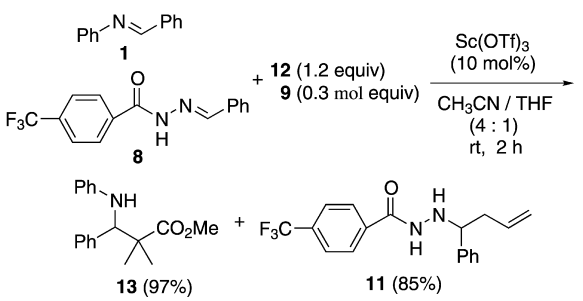


Scheme 3.

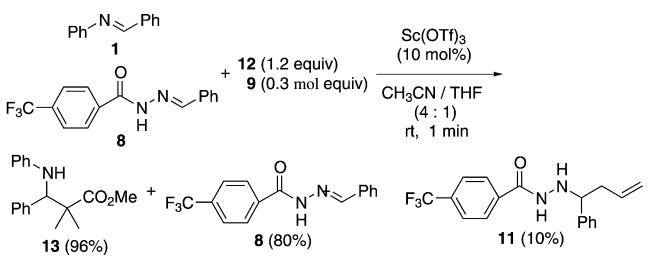
yields (Scheme 3).[10] On the other hand, only a trace amount of product **15** derived from **12** was detected upon decreasing the amount of this reagent down to 0.2 equiv. It follows from the above results that under standard conditions, **12** reacted with **1** very rapidly so as to consume this substrate completely before initiation of the reaction of **9**. At this stage, the molar ratio of **12**/**9** was 0.2:0.3 and, hence, the remaining substrate **8** started to react with **9** exclusively. It is concluded therefore that the substrate selectivity in the shotgun process could be improved kinetically by adjusting the ratio of reagents even if the elementary reactions are not selective.



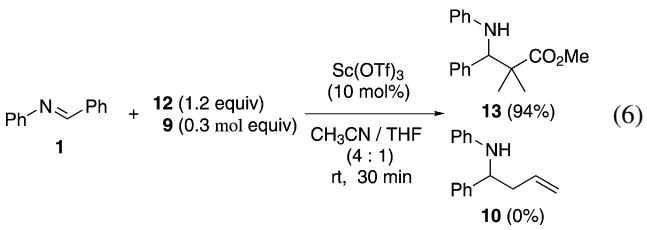
(3)



(4)



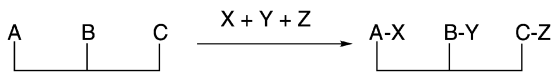
(5)



(6)

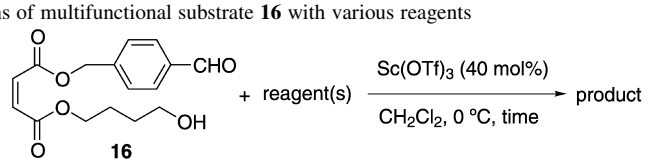
2.3. Functionally controlled shotgun process

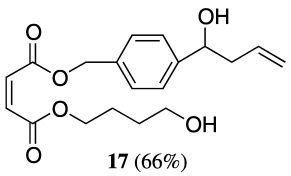
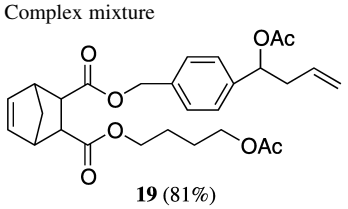
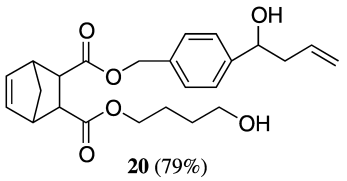
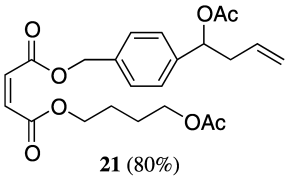
A triple-track shotgun process where three reactions proceed on three different reaction sites (Scheme 4) is far more complicated than the aforementioned double-track protocol. In addition, interactions between substrate functions and reagents occur more frequently to modify the elementary reactions. We picked substrate **16** to test the feasibility of the triple-track version (Table 3). Under catalysis of $Sc(OTf)_3$, the three functions involved in **16** are known to undergo smoothly the following reactions: allylation of aldehyde with tetraallytin (**9**),[11] Diels–Alder reaction of α,β-unsaturated ester with cyclopentadiene (**5**),[4] and acetylation of hydroxy group with acetic anhydride (**18**),[12] respectively. Notwithstanding, **16** failed to react with these reagents satisfactorily. Upon treatment with **9** (entry 1), only a 66% yield of allylation product **17** was obtained while complex mixtures of unidentifiable materials appeared by exposure to **5** and **18** (entires 2 and 3). It should be noted that the yields of representative simple elementary reactions under the same conditions were 85% for allylation of benzaldehyde, 99% for Diels–Alder reaction with dimethyl maleate, and 99% for acetylation of octanol. These results imply that the elementary reactions are influenced by coexisting functional groups. In sharp contrast to the reactions given in entries 1–3, addition of the three reagents in one shot provided a single product **19** in



Scheme 4.

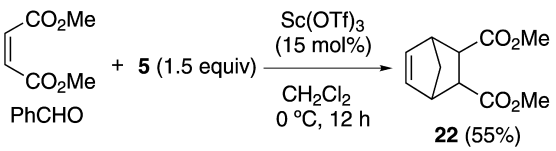
Table 3. $Sc(OTf)_3$-catalyzed reactions of multifunctional substrate **16** with various reagents



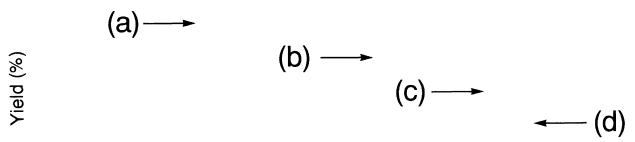
Entry	Reagent(s)	Time (h)	Product(s)[a]
1	**9** (0.3 mol equiv.)	12	 **17** (66%)
2	**5** (3 equiv.)	12	Complex mixture
3	Ac_2O **18** (2 equiv.)	12	Complex mixture
4	**5** (3 equiv.) **9** (0.3 mol equiv.) **18** (2 equiv.)	24	 **19** (81%)
5	**5** (3 equiv.) **9** (0.3 mol equiv.)	24	 **20** (79%)
6	**9** (0.3 mol equiv.) **18** (2 equiv.)	24	 **21** (80%)
7	**5** (3 equiv.) **18** (2 equiv.)	24	Complex mixture

[a] Isolated yield after column chromatography.

81% yield, which corresponds to a 93% yield in average for each reaction (entry 4).[13] When **16** was exposed to a mixture of reagents **5/9** or **9/18**, reasonable yields of the corresponding products as a result of the two reactions were obtained (entries 5 and 6). On the other hand, no smooth reactions took place with a combination of reagents **5/18** (entry 7). Obviously, the shotgun process occurred successfully when the allylation reaction was involved, and hence, it was postulated that an aldehyde function retarded the Diels–Alder and acetylation reactions and rapid consumption of the aldehyde revived the remaining two reactions in the shotgun process. This was confirmed by intermolecular reactions. The yields of Diels–Alder reaction and acetylation were decreased in the presence of benzaldehyde (Eqs. (7) and (8)) while addition of **9** to consume the aldehyde gave rise to recovery of the yields (Eqs. (9) and (10)). Figure 1 shows a profile of the time-conversion relationship in the triple-track shotgun process.[14,15] Remarkably, the allylation finished after 15 s and, then, the Diels–Alder reaction and acetylation followed. As such, it is now apparent that the smooth shotgun process resulted from the rapid consumption of the aldehyde function so that the Diels–Alder and acetylation reactions were freed from retardation by this function.



(7)



(a) **(17, 19, 20, 21, 26-29)**
(b) **(19, 20, 26, 28)**
(c) **(19, 21, 26, 27)**
(d) **(19, 21, 28, 29)**

The following compounds were involved in the transient reaction products although **19** was obtained finally as the sole product.

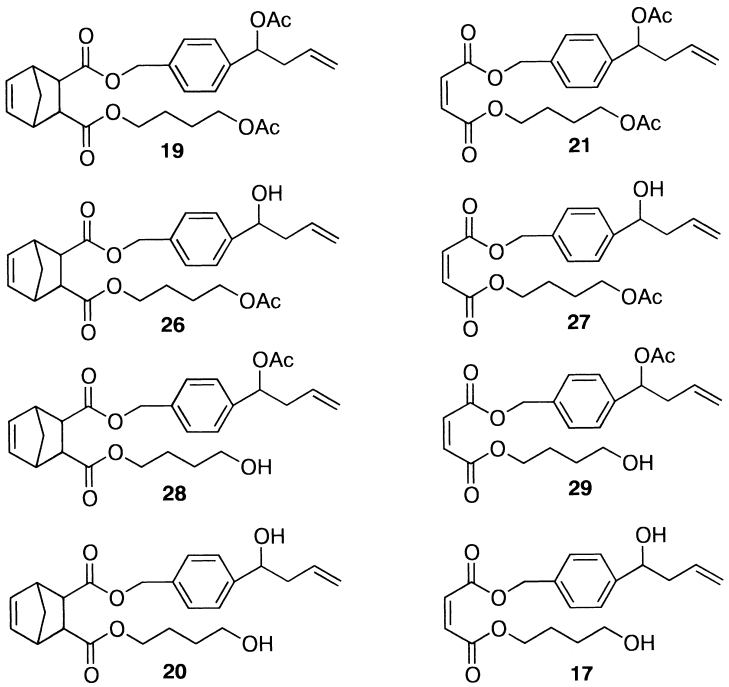
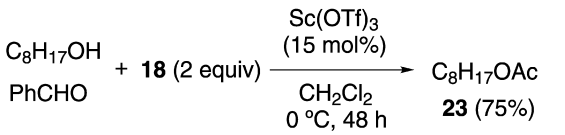
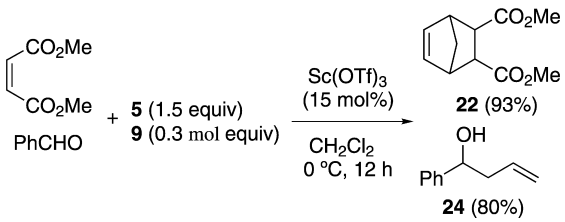


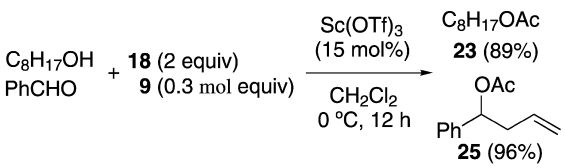
Figure 1. Time-conversion curves of the triple-track shotgun process.



(8)

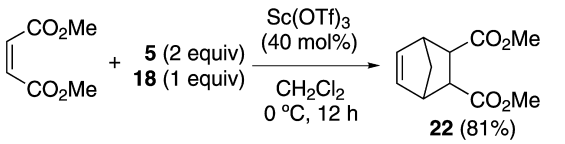


(9)

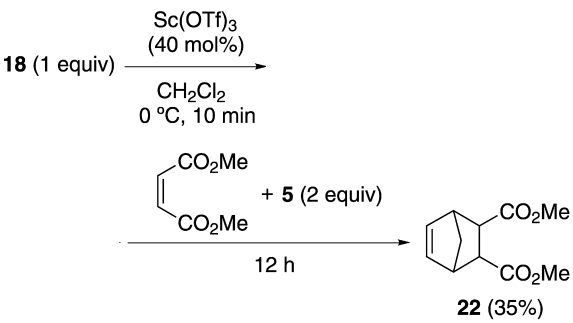


(10)

The reactions proceeding in parallel are proved to be retarded by not only the functional groups of the substrates but also the coexisting reagents. For instance, when the Diels–Alder reaction between **5** and dimethyl malonate was run in the presence of acetic anhydride **18**, the color of the reaction mixture turned black and the yield was decreased to some extent (Eq. (11)). TLC analysis suggested that cyclopentadiene had polymerized.[16] The yield was further decreased to 35% upon treatment of $Sc(OTf)_3$ with **18** for 10 min prior to addition of **5** and dimethyl malonate (Eq. (12)). As we disclosed previously, combining $Sc(OTf)_3$ and **18** gave rise to a new catalytic species,[17] which induced polymerization of **5**. Apparently, constant consumption of **18** by concurrent acetylation also served for the smooth Diels–Alder reaction in the shotgun process. It was revealed already that this newly created scandium species is responsible for acceleration of allylation. Thus, acetic anhydride also served for increasing the rate of the allylation reaction to accelerate consumption of aldehyde so as to set the Diels–Alder reaction and acetylation free from retardation. The enhanced rate of acetylation, then, served for decreasing the suppressing effect of acetic anhydride on the Diels–Alder reaction.

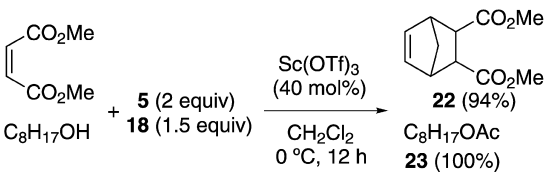


(11)

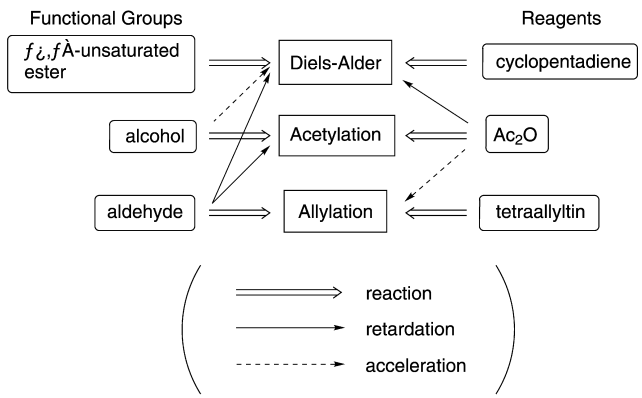


(12)

An additional example of the influence by reagents was given in Eq. (13). When the reaction 11 was conducted in the presence of octanol, the yield of the Diels–Alder adduct was improved to 94%. Since addition of octyl acetate in place of octanol gave rise to no influence and addition of acetic acid lowered the yield, the species responsible for increasing the yield in the reaction mixture is unambiguously assigned to the octanol. As a whole, the synergistic relationship between the functional groups and reagents involved in the present triple-track shotgun process is summarized in Scheme 5.



(13)



Scheme 5.

In conclusion, we have demonstrated three types of the shotgun processes. In all of these processes, the perfect recognition between concurrent different reactions on the separate reaction sites is feasible. Even in the cases where simple shotgun processes are not applicable, the recognition can be achieved by adjusting the substrate ratio or by balancing functional groups. This potentially expands the scope of the shotgun process and we believe that the concept disclosed herein will find a wide range of applications for the simplified processes. Notably, it follows from the functionally controlled shotgun process that integration of reactions does not necessarily lead to simple superimposition of the original reactions. Such effect alters innate features of respective reactions but would be of great help for improving selectivity if appropriately used. This is an important aspect to be taken into account for running reactions in parallel.

3. Experimental

3.1. Competition reaction (Table 1, entry 1)

To a suspension of $Yb(OTf)_3$ (124 mg, 0.20 mmol) in CH_2Cl_2 (4.0 mL) was added a CH_2Cl_2 solution (1.0 mL) containing **1** (181 mg, 1.0 mmol) and **2** (158 mg, 1.0 mmol) at 0°C. Then, **3** (0.23 mL, 1.20 mmol) was added and the solution was stirred at 0°C for 6 h. Saturated aqueous $NaHCO_3$ solution was added and the mixture was extracted with EtOAc. The organic layer was washed with brine and dried Na_2SO_4. The crude product obtained after

filtration and evaporation was purified by column chromatography on silica gel (1:1 hexane/EtOAc) to give **4** (234 mg, 94%).

3.2. Competition reaction (Table 1, entry 2)

The same procedure of Section 3.1 was conducted using **5** (0.17 mL, 2.0 mL) in place of **3**. After 24 h, GLC analysis of the crude product thus obtained indicated formation of **6** in 5% yield. Then, column chromatography of the crude product on silica gel (17:3 hexane/EtOAc) afforded **7** (222 mg, 99%).

3.3. Shotgun process (Table 1, entry 3)

To a suspension of $Yb(OTf)_3$ (124 mg, 0.20 mmol) in CH_2Cl_2 (4.0 mL) was added a CH_2Cl_2 solution (1.0 mL) containing **1** (181 mg, 1.0 mmol) and **2** (158 mg, 1.0 mmol) at 0°C. Then, a CH_2Cl_2 solution (1 mL) containing **3** (0.23 mL, 1.20 mmol) and **5** (0.17 mL, 2.0 mL) was added and the solution was stirred at 0°C for 24 h. After aqueous workup as described above, the crude product was purified by column chromatography on silica gel to give **7** (215 mg, 96%) (17:3 hexane/EtOAc) and **4** (229 mg, 92%) (1:1 hexane/EtOAc), respectively.

3.4. Competition reaction (Eq. (1))

To a suspension of $Yb(OTf)_3$ (124 mg, 0.20 mmol) in CH_2Cl_2 (4.0 mL) was added a CH_2Cl_2 solution (1.0 mL) of **1** (181 mg, 1.0 mmol) at 0°C. Then, a CH_2Cl_2 solution (1.0 mL) of **3** (0.23 mL, 1.20 mmol) and **5** (0.17 mL, 2.0 mL) was added and the solution was stirred at 0°C for 5 min. After aqueous workup as described above, the crude product was purified by column chromatography on silica gel (1:1 hexane/EtOAc) to give **4** (239 mg, 96%).

3.5. Competition reaction (Table 2, entry 1)

To a mixed solution of CH_3CN (19.0 mL) and THF (5.0 mL) containing **1** (91 mg, 0.50 mmol), **8** (146 mg, 0.50 mmol) and **3** (0.12 mL, 0.60 mmol) was added a CH_3CN solution (1.0 mL) of $Sc(OTf)_3$ (25 mg, 0.05 mmol) at room temperature. The mixture was stirred for 30 min. After aqueous workup as described above, the crude product was purified by column chromatography on silica gel (1:1 hexane/EtOAc) to give **4** (120 mg, 96%).

3.6. Competition reaction (Table 2, entry 2)

A similar reaction employing **1** (91 mg, 0.50 mmol), **8** (146 mg, 0.50 mmol) and **9** (0.04 mL, 0.15 mmol) furnished **10** (28 mg, 25%) (column chromatography on silica gel; 19:1 hexane/EtOAc) and **11** (122 mg, 73%) (column chromatography on silica gel; 17:3 hexane/EtOAc), respectively.

3.7. Shotgun process (Table 2, entry 3; Eq. (2))

To a mixed solution of CH_3CN (19.0 mL) and THF (5.0 mL) containing **1** (91 mg, 0.50 mmol), **8** (146 mg, 0.50 mmol), **3** (0.12 mL, 0.60 mmol) and **9** (0.04 mL, 0.15 mmol) was added a CH_3CN solution (1.0 mL) of $Sc(OTf)_3$ (25 mg, 0.05 mmol) at room temperature. The mixture was stirred for 15 h. After aqueous workup as described above, the crude product was purified by column chromatography on silica gel to give **11** (159 mg, 95%) (17:3 hexane/EtOAc) and **4** (120 mg, 96%) (1:1 hexane/EtOAc), respectively. When the reaction was quenched after 1 min, **4** (94%) and **11** (6%) were obtained along with unreacted **8** (89%).

3.8. Competition reaction (Eq. (3))

To a mixed solution of CH_3CN (19.0 mL) and THF (5.0 mL) containing **1** (91 mg, 0.50 mmol), **8** (146 mg, 0.50 mmol) and **12** (0.12 mL, 0.60 mmol) was added a CH_3CN solution (1.0 mL) of $Sc(OTf)_3$ (25 mg, 0.05 mmol) at room temperature. The mixture was stirred for 30 min. After aqueous workup as described above, the crude product was purified by column chromatography on silica gel to give **13** (141 mg, 99%) (19:1 hexane/EtOAc) and **14** (24 mg, 12%) (4:1 hexane/EtOAc), respectively.

3.9. Shotgun process (Eqs. (4) and (5); Scheme 2)

To a mixed solution of CH_3CN (19.0 mL) and THF (5.0 mL) containing **1** (91 mg, 0.50 mmol), **8** (146 mg, 0.50 mmol), **12** (0.12 mL, 0.60 mmol) and **9** (0.04 mL, 0.15 mmol) was added a CH_3CN solution (1.0 mL) of $Sc(OTf)_3$ (25 mg, 0.05 mmol) at room temperature. The mixture was stirred for 2 h. After aqueous workup as described above, the crude product was purified by column chromatography on silica gel to give **13** (138 mg, 97%) (19:1 hexane/EtOAc) and **11** (142 mg, 85%) (17:3 hexane/EtOAc), respectively. When the reaction was quenched after 1 min, **13** (96%) and **11** (10%) were obtained along with unreacted **8** (80%).

3.10. Competition reaction (Eq. (6))

To a mixed solution of CH_3CN (19.0 mL) and THF (5.0 mL) containing **1** (91 mg, 0.50 mmol), **12** (0.12 mL, 0.60 mmol) and **9** (0.04 mL, 0.15 mmol) was added a CH_3CN solution (1.0 mL) of $Sc(OTf)_3$ (25 mg, 0.05 mmol) at room temperature. The mixture was stirred for 30 min. After aqueous workup as described above, the crude product was purified by column chromatography on silica gel (19:1 hexane/EtOAc) to give **13** (133 mg, 94%).

3.11. Competition reaction (Scheme 3)

To a mixed solution of CH_3CN (19.0 mL) and THF (5.0 mL) containing **8** (146 mg, 0.50 mmol), **12** (0.12 mL, 0.60 mmol) and **9** (0.04 mL, 0.15 mmol) was added a CH_3CN solution (1.0 mL) of $Sc(OTf)_3$ (25 mg, 0.05 mmol) at room temperature. The mixture was stirred for 2 h. After aqueous workup as described above, the crude product was purified by column chromatography on silica gel to give **11** (78 mg, 47%) (17:3 hexane/EtOAc) and **15** (56 mg, 31%) (17:3 hexane/EtOAc). When 0.2 equiv. of **12** was employed, **11** (87%) and only a trace amount (<1%) of **15** were obtained.

3.12. Reaction of 16 with 9 (Table 3, entry 1)

To a suspension of $Sc(OTf)_3$ (98 mg, 0.20 mmol) in CH_2Cl_2 (5.0 mL) were added a CH_2Cl_2 solution (1.0 mL) of **16**

(153 mg, 0.50 mmol) and a CH_2Cl_2 (1.0 mL) solution of **9** (0.04 mL, 0.15 mmol) in succession at 0°C. The reaction mixture was stirred for 12 h at this temperature. After water had been added, the reaction mixture was extracted with EtOAc. The combined organic layer was washed with 1N HCl, sat. aqueous $NaHCO_3$ and brine. The crude product after drying (Na_2SO_4), filtration and evaporation was purified by column chromatography on silica gel (2:3 hexane/EtOAc) to give **17** (115 mg, 66%).

3.13. Shotgun process (Table 3, entry 4)

To a suspension of $Sc(OTf)_3$ (98 mg, 0.20 mmol) in CH_2Cl_2 (5.0 mL) were added a CH_2Cl_2 solution (1.0 mL) of **16** (153 mg, 0.50 mmol) and a CH_2Cl_2 solution (1.0 mL) containing **5** (0.12 mL, 1.50 mmol), **9** (0.04 mL, 0.15 mmol) and **18** (0.09 mL, 1.0 mmol) in succession at 0°C. The reaction mixture was stirred for 24 h at this temperatue. After workup as done in Section 3.12, the crude product was purified by column chromatography on silica gel (4:1 hexane/EtOAc) to give **19** (202 mg, 81%).

3.14. Reaction of 16 with 5 and 9 (Table 3, entry 5)

To a suspension of $Sc(OTf)_3$ (98 mg, 0.20 mmol) in CH_2Cl_2 (5.0 mL) were added a CH_2Cl_2 solution (1.0 mL) of **16** (153 mg, 0.50 mmol) and a CH_2Cl_2 solution (1.0 mL) containing **5** (0.12 mL, 1.50 mmol) and **9** (0.04 mL, 0.15 mmol) in succession at 0°C. The reaction mixture was stirred for 24 h at this temperatue. After workup as done in Section 3.12, the crude product was purified by column chromatography on silica gel (2:3 hexane/EtOAc) to give **20** (164 mg, 79%).

3.15. Reaction of 16 with 9 and 18 (Table 3, entry 6)

A similar reaction employing **9** (0.04 mL, 0.15 mmol) and **18** (0.09 mL, 1.00 mmol) furnished **21** (173 mg, 80%) after column chromatography on silica gel (7:3 hexane/EtOAc).

3.16. Diels–Alder reaction in the presence of aldehyde (Eq. (7))

To a CH_2Cl_2 (3.0 mL) of suspension of $Sc(OTf)_3$ (74 mg, 0.15 mmol) was added a CH_2Cl_2 solution (1.0 mL) of dimethyl maleate (144 mg, 1.00 mmol) and benzaldehyde (106, mg, 1.00 mmol) followed by a CH_2Cl_2 solution (1.0 mL) of **5** (0.12 mL, 1.50 mmol) at 0°C. The reaction mixture was stirred for 12 h at this temperature. After workup as described in Section 3.1, GLC analysis of the crude product indicated the formation of **22** in 55% yield.

3.17. Acetylation in the presence of aldehyde (Eq. (8))

To a CH_2Cl_2 (3.0 mL) of suspension of $Sc(OTf)_3$ (74 mg, 0.15 mmol) was added a CH_2Cl_2 solution (1.0 mL) of octanol (130 mg, 1.00 mmol) and benzaldehyde (106 mg, 1.00 mmol) followed by a CH_2Cl_2 solution (1.0 mL) of **18** (0.19 mL, 2.0 mmol) at 0°C. The reaction mixture was stirred for 48 h at this temperature. After workup as described in Section 3.1, GLC analysis of the crude product indicated the formation of **23** in 75% yield.

3.18. Shotgun process (Eq. (9))

To a CH_2Cl_2 suspension (3.0 mL) of $Sc(OTf)_3$ (74 mg, 0.15 mmol) was added a CH_2Cl_2 solution (1.0 mL) containig dimethyl maleate (144 mg, 1.00 mmol) and benzaldehyde (106 mg, 1.00 mmol) followed by a CH_2Cl_2 solution (1.0 mL) containing **5** (0.12 mL, 1.50 mmol) and **9** (0.07 mL, 0.30 mmol) at 0°C. The reaction mixture was stirred for 12 h at this temperature. After workup as described in Section 3.12, GLC analysis of the crude product indicated the formation of **22** and **24** in 93 and 80% yields, respectively.

3.19. Shotgun process (Eq. (10))

A similar reaction employing octanol (130 mg, 1.00 mmol), benzaldehyde (106 mg, 1.00 mmol), **18** (0.19 mL, 2.00 mmol) and **9** (0.07 mL, 0.30 mmol) provided **23** and **25** in 89 and 96% yields (on the basis of GLC), respectively.

3.20. Diels–Alder reaction in the presence of Ac_2O (Eq. (11))

To a CH_2Cl_2 suspension (3.0 mL) of $Sc(OTf)_3$ (197 mg, 0.40 mmol) was added a CH_2Cl_2 solution (1.0 mL) of dimethyl maleate (144 mg, 1.00 mmol) followed by a CH_2Cl_2 solution (1.0 mL) containing **5** (0.17 mL, 2.00 mmol) and **18** (0.09 mL, 1.00 mmol) at 0°C. The reaction mixture was stirred for 12 h at this temperature. After workup as described in Section 3.1, GLC analysis of the crude product indicated the formation of **22** in 81% yield.

3.21. Diels–Alder reaction after mixing of $Sc(OTf)_3$ and Ac_2O (Eq. (12))

A CH_2Cl_2 suspension (4.0 mL) containing $Sc(OTf)_3$ (197 mg, 0.40 mmol) and **18** (0.09 mL, 1.00 mmol) was stirred at 0°C for 10 min. A CH_2Cl_2 solution (1.0 mL) of dimethyl maleate (144 mg, 1.00 mmol) and **5** (0.17 mL, 2.00 mmol) was added, and the mixture was stirred at 0°C for 12 h. After workup as above, GLC analysis of the crude product indicated the formation of **22** in 35% yield.

3.22. Determination of time-conversion relationship in triple-track shotgun process (Fig. 1)

The shotgun reaction under the standard conditions was quenched with Me_2NNH_2. Column chromatography provided four fractions consisting of mixtures of **19/21**, **26/27**, **28/29**, and **17/20**, respectively. The yield of each product in the mixtures was determined on the basis of NMR spectra.

3.23. Shotgun process (Eq. (13))

To a CH_2Cl_2 (3.0 mL) suspension containing $Sc(OTf)_3$ (197 mg, 0.40 mmol) was added a CH_2Cl_2 solution (1.0 mL) of dimethyl maleate (144 mg, 1.00 mmol) and octanol (130 mg, 1.00 mmol) followed by a CH_2Cl_2 solution (1.0 mL) of **5** (0.17 mL, 2.00 mmol) and **18** (0.14 mL, 1.50 mmol). The mixture was stirred at 0°C for 12 h. After workup as done in Section 3.1, GLC analysis of the crude product indicated the formation of **22** and **23** in 94 and 100% yields, respectively (based on GLC).

3.24. Characterization of new compounds

The new compounds were characterized as follows except the following known compounds (**4**,[3] **6**,[3] **7**,[4] **8**,[8] **10**,[5] **13**,[7] **14**,[8] **22**,[18] **24**[19] and **25**[20]) and commercially available **23**.

3.24.1. Compound 11. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50–2.54 (m, 2H), 4.18 (t, J=7.1 Hz, 1H), 5.13–5.24 (m, 2H), 5.28 (br, 1H), 5.79–5.93 (m, 1H), 7.28–7.41 (m, 5H), 7.64 (d, J=8.4 Hz, 2H), 7.69 (d, J=8.4 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.3, 63.8, 118.1, 123.5 (q, J_{C-F}=272.9 Hz), 125.5 (q, J_{C-F}=3.6 Hz), 127.3, 127.6, 127.8, 128.5, 133.3 (q, J_{C-F}=32.7 Hz), 134.3, 136.0, 141.3, 165.9. HRMS (EI) for $C_{18}H_{17}F_3N_2O$ calcd 334.1293 found 334.1278.

3.24.2. Compound 15. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (s, 3H), 1.27 (s, 3H), 4.47 (d, J=6.1 Hz, 1H), 6.16 (d, J=6.6 Hz, 1H), 7.38–7.46 (m, 5H), 7.70 (d, J=8.6 Hz, 2H), 7.76 (d, J=8.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.8, 21.4, 47.4, 67.8, 123.6 (q, J_{C-F}=272.6 Hz), 124.9 (q, J_{C-F}=3.6 Hz), 127.4, 128.5, 128.6, 129.3, 133.4 (q, J_{C-F}=32.6 Hz), 134.5, 136.4, 164.1, 174.5. HRMS (EI) for $C_{19}H_{17}F_3N_2O_2$ calcd 362.1242 found 362.1223.

3.24.3. Compound 16. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.56–1.79 (m, 4H), 1.88 (br, 1H), 3.65 (t, J=6.2 Hz, 2H), 4.18 (t, J=6.4 Hz, 2H), 5.30 (s, 2H), 6.29 (d, J=12.0 Hz, 1H), 6.34 (d, J=12.0 Hz, 1H), 7.55 (d, J=8.2 Hz, 2H), 7.90 (d, J=8.2 Hz, 2H), 10.02 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.8, 28.9, 62.1, 65.2, 66.1, 128.4, 128.8, 129.9, 130.8, 136.1, 141.8, 164.8, 165.1, 191.8. HRMS (EI) for $C_{16}H_{18}O_6$ calcd 306.1103 found 306.1093.

3.24.4. Compound 17. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48–1.70 (m, 4H), 2.37 (br, 1H), 2.42–2.56 (m, 2H), 3.60 (t, J=6.2 Hz, 2H), 4.11 (dt, J=2.1, 6.5 Hz, 2H), 4.75 (dd, J=5.3, 7.5 Hz, 1H), 5.13–5.20 (m, 4H), 5.74–5.87 (m, 1H), 6.24 (d, J=12.0 Hz, 1H), 6.29 (d, J=12.0 Hz, 1H), 7.37 (s, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.6, 28.5, 43.4, 61.6, 65.0, 66.7, 72.8, 117.9, 125.9, 128.4, 128.7, 130.4, 134.0, 134.2, 144.3, 164.8, 165.2. HRMS (EI) for $C_{19}H_{24}O_6$ calcd 348.1573 found 348.1598.

3.24.5. Compound 19. Mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (d, J=8.4 Hz, 1H), 1.48 (dt, J=1.8, 8.7 Hz, 1H), 1.63–1.66 (m, 4H), 2.04 (s, 3H), 2.07 (s, 3H), 2.49–2.69 (m, 2H), 3.17–3.18 (m, 2H), 3.29 (dd, J=3.1, 10.3 Hz, 1H), 3.34 (dd, J=2.7, 10.2 Hz, 1H), 3.88–4.08 (m, 4H), 4.95 (d, J=12.5 Hz, 1H), 5.03–5.11 (m, 3H), 5.62–5.76 (m, 1H), 5.79 (dd, J=6.1, 7.5 Hz, 1H), 6.23 (d, J=6.4 Hz, 1H), 6.26 (d, J=7.0 Hz, 1H), 7.31 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.8, 21.0, 25.0, 25.2, 40.5, 46.2, 46.3, 48.00, 48.04, 48.6, 63.7, 63.8, 65.77, 65.78, 74.7, 118.0, 126.5, 128.21, 128.25, 133.0, 134.71, 134.72, 134.8, 135.6, 139.93, 139.94, 170.0, 170.9, 172.1, 172.3. HRMS (EI) for $C_{28}H_{34}O_8$ calcd 498.2254 found 498.2277.

3.24.6. Compound 20. Mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (d, J=8.6 Hz, 1H), 1.43–1.60 (m, 5H), 2.42–2.57 (m, 2H), 3.14–3.19 (m, 2H), 3.27 (ddd, J=0.8, 3.1, 10.2 Hz, 1H), 3.34 (ddd, J=2.2, 3.1, 10.1 Hz, 1H), 3.56 (t, J=6.1 Hz, 2H), 3.80–3.99 (m, 2H), 4.73 (dd, J=5.7, 7.3 Hz, 1H), 5.02 (s, 2H), 5.13–5.20 (m, 2H), 5.73–5.87 (m, 1H), 6.23–6.27 (m, 2H), 7.31 (d, J=8.4 Hz, 2H), 7.35 (d, J=8.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.7, 28.64, 28.65, 43.48, 43.50, 46.10, 46.12, 46.13, 47.96, 48.10, 48.12, 48.5, 61.7, 64.0, 65.88, 65.91, 72.9, 117.9, 125.83, 125.84, 128.18, 128.25, 134.3, 134.7, 134.9, 144.0, 172.2, 172.4. HRMS (EI) for $C_{24}H_{30}O_6$ calcd 414.2042 found 414.2061.

3.24.7. Compound 21. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.66–1.75 (m, 4H), 2.05 (s, 3H), 2.07 (s, 3H), 2.51–2.67 (m, 2H), 4.08 (t, J=5.9 Hz, 2H), 4.16 (t, J=5.9 Hz, 2H), 5.04–5.10 (m, 2H), 5.20 (s, 2H), 5.65–5.73 (m, 1H), 5.79 (dd, J=6.1, 7.6 Hz, 1H), 6.26 (d, J=11.9 Hz, 1H), 6.28 (d, J=11.9 Hz, 1H), 7.34 (d, J=8.3 Hz, 2H), 7.36 (d, J=8.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.8, 21.0, 24.9, 25.0, 40.5, 63.7, 64.6, 66.6, 74.6, 118.0, 126.6, 128.5, 129.1, 130.3, 133.0, 134.7, 140.3, 164.8, 165.1, 170.0, 170.9. HRMS (EI) for $C_{23}H_{28}O_8$ calcd 432.1784 found 432.1760.

3.24.8. Compound 26. Mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (d, J=8.6 Hz, 1H), 1.48 (dt, J=1.8, 8.6 Hz, 1H), 1.59–1.63 (m, 4H), 2.03 (s, 3H), 2.28 (br, 1H), 2.42–2.55 (m, 2H), 3.15–3.20 (m, 2H), 3.28 (dd, J=2.9, 10.1 Hz, 1H), 3.34 (dd, J=3.0, 10.2 Hz, 1H), 3.88–4.07 (m, 4H), 4.72–4.77 (m, 1H), 4.98 (d, J=12.3 Hz, 1H), 5.07 (d, J=12.3 Hz, 1H), 5.12–5.20 (m, 2H), 5.74–5.88 (m, 1H), 6.22–6.27 (m, 2H), 7.29–7.36 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 25.1, 25.2, 43.8, 46.4, 48.17, 48.20, 48.7, 63.8, 64.0, 66.0, 72.9, 118.4, 125.9, 128.3, 134.3, 134.86, 134.91, 135.2, 144.0, 171.2, 172.2, 172.4. HRMS (EI) for $C_{26}H_{32}O_7$ calcd 456.2148 found 456.2159.

3.24.9. Compound 27. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.65–1.72 (m, 4H), 2.04 (s, 3H), 2.23 (br, 1H), 2.45–2.55 (m, 2H), 4.03 (t, J=5.9 Hz, 2H), 4.15 (t, J=5.9 Hz, 2H), 4.75 (dd, J=5.2, 7.6 Hz, 1H), 5.14–5.19 (m, 2H), 5.21 (s, 2H), 5.76–5.85 (m, 1H), 6.26 (d, J=11.9 Hz, 1H), 6.28 (d, J=11.9 Hz, 1H), 7.37 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.9, 24.96, 25.03, 43.7, 63.8, 64.7, 66.8, 72.8, 118.4, 126.0, 128.5, 129.1, 130.3, 134.2, 144.4, 164.8, 165.2, 171.1. HRMS (EI) for $C_{21}H_{26}O_7$ calcd 390.1679 found 390.1666.

3.24.10. Compound 28. Mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (d, J=8.6 Hz, 1H), 1.46–1.65 (m, 5H), 2.07 (s, 3H), 2.48–2.69 (m, 2H), 3.15–3.19 (m, 2H), 3.26–3.36 (m, 2H), 3.61 (t, J=5.5 Hz, 2H), 3.86–4.05 (m, 2H), 4.97 (d, J=12.5 Hz, 1H), 5.03–5.11 (m, 3H), 5.62–5.80 (m, 2H), 6.25 (t, J=1.7 Hz, 2H), 7.31 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 24.9, 29.1, 40.6, 46.28, 46.36, 46.38, 48.18, 48.20, 48.6, 62.2, 64.16, 64.18, 65.8, 65.9, 74.88, 74.90, 118.1, 126.6, 128.2, 128.4, 133.1, 134.78, 134.81, 134.88, 134.91, 135.68, 135.70, 139.97, 140.01, 170.2, 170.3, 172.3, 172.4. HRMS (EI) for $C_{26}H_{32}O_7$ calcd 456.2148 found 456.2170.

3.24.11. Compound 29. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53–1.76 (m, 4H), 2.07 (s, 3H), 2.49–2.69 (m, 2H), 3.63 (t, J=6.2 Hz, 2H), 4.15 (t, J=6.4 Hz, 2H), 5.04–5.11 (m, 2H), 5.20 (s, 2H), 5.62–5.76 (m, 1H), 5.78 (dd, J=6.1, 7.6 Hz, 1H), 6.24 (d, J=12.0 Hz, 1H), 6.29 (d, J=12.0 Hz, 1H), 7.33 (d, J=8.7 Hz, 2H), 7.36 (d, J=8.7 Hz, 2H). ^{13}C NMR

(75 MHz, $CDCl_3$) δ 21.1, 24.8, 28.9, 40.6, 62.1, 65.1, 66.7, 74.9, 118.1, 126.7, 128.6, 128.9, 130.6, 133.0, 134.8, 140.4, 164.9, 165.2, 170.3. HRMS (EI) for $C_{21}H_{26}O_7$ calcd 390.1679 found 390.1679.

References

1. Nagano, Y.; Orita, A.; Otera, J. *Tetrahedron* **2002**, *58*, 8211.
2. A part of this study appeared in a preliminary form: Orita, A.; Nagano, Y.; Nakazawa, K.; Otera, J. *Synlett* **2000**, 599.
3. Kobayashi, S.; Ishitani, H.; Nagayama, S. *Synthesis* **1995**, 1195.
4. (a) Kobayashi, S.; Araki, M.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3758. (b) Kobayashi, S.; Hachiya, I.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1993**, *34*, 3755. (c) Kobayashi, S.; Hachiya, I.; Takahori, T.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1992**, *33*, 6815.
5. For reaction of imine with allyltributyltin: Bellucci, C.; Cozzi, P. G.; Umani-Ronchi, A. *Tetrahedron Lett.* **1995**, *36*, 7289.
6. Kobayashi, S.; Sugita, K.; Oyamada, H. *Synlett* **1999**, 138.
7. Kobayashi, S.; Araki, M.; Ishitani, H.; Nagayama, S.; Hachiya, I. *Synlett* **1995**, 233.
8. (a) Kobayashi, S.; Furuta, T.; Sugita, K.; Oyamada, H. *Synlett* **1998**, 1019. (b) Oyamada, H.; Kobayashi, S. *Synlett* **1998**, 249.
9. (a) Chen, J.; Otera, J. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 91. (b) Chen, J.; Otera, J. *Tetrahedron Lett.* **1998**, *39*, 1767. (c) Chen, J.; Sakamoto, K.; Orita, A.; Otera, J. *Tetrahedron* **1998**, *54*, 8411.
10. The reaction of **8** with **12** provided cyclized product **15** under these conditions.
11. (a) Kobayashi, S.; Wakabayashi, T.; Oyamada, H. *Chem. Lett.* **1997**, 831. (b) Hachiya, I.; Kobayashi, S. *J. Org. Chem.* **1993**, *58*, 6958.
12. (a) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4560. (b) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 4413.
13. With catalyst concentration lower than 40%, the Diels–Alder reaction did not complete.
14. The reaction was quenched with Me_2NNH_2 because allylation with **9** takes place in the presence of water.[11]
15. For analysis of the products, see Section 3.
16. Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Oxford, 1990.
17. Nagano, Y.; Orita, A.; Otera, J. *Adv. Synth. Catal.* **2003**, *345*, 643.
18. Pagni, R. M.; Kabalka, G. W.; Hondrogiannis, G.; Bains, S.; Anosike, P.; Kurt, R. *Tetrahedron* **1993**, *49*, 6743.
19. Davis, A. P.; Jaspars, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2111.
20. Falck, J. R.; Bhatt, R. K.; Ye, J. *J. Am. Chem. Soc.* **1995**, *117*, 5973.