Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 61 (2005) 2217–2231

Highly chemoselective hydrogenation method using novel finely dispersed palladium catalyst on silk-fibroin: its preparation and activity

Takashi Ikawa, Hironao Sajiki* and Kosaku Hirota*

Laboratory of Medicinal Chemistry, Gifu Pharmaceutical University, 5-6-1 Mitahora-higashi, Gifu 502-8585, Japan

Received 25 October 2004; accepted 29 November 2004

Available online 19 January 2005

Abstract—A palladium–fibroin complex (Pd/Fib) was prepared by soaking silk-fibroin in MeOH solution of $Pd(OAc)_2$ for 2 days (under Ar atmosphere)—4 days (under air). $Pd(OAc)_2$ was gradually absorbed by fibroin and the rapid reduction of fibroin conjugated $Pd(OAc)_2$ proceeded with MeOH as a reductant at room temperature to be the Pd(0) complex. Pd/Fib catalyzed chemoselective hydrogenation of acetylenes, olefins and azides in the presence of aromatic ketones and aldehydes, halides, *N*-Cbz protective groups and benzyl esters which are readily hydrogenated using Pd/C or Pd/C(en) as a catalyst.

1. Introduction

Catalytic hydrogenation using a heterogeneous catalyst has been a powerful tool for functional group transformation in both the laboratory and industrial plant.[1] Pd/C, a heterogeneous catalyst, has many advantages over homogeneous catalysts, such as stability of the catalysts, ease of separation from the reaction mixture upon completion of the reaction, a good possibility of recyclability, cost reduction and high catalytic ability. However, the high catalytic activity of Pd/C makes it difficult to attain chemoselective reduction among some reducible functional groups. Recently, we reported several chemoselective hydrogenation methods using a Pd/C-ethylenediamine complex [Pd/C(en)].[2,3] Further development of novel catalysts for chemoselective hydrogenation methods will reinforce the versatility of synthetic processes.

On the other hand, the silk secreted from the silk gland of the silkworm *Bombyx mori* is composed of two principal components of proteins, fibroin and sericins, characterized by their solubility and stability in hot water, which enables the industrial degumming of the silk threads. Recently, fibroin and sericines have come to be considered a useful bio-material accounting for a wide variety of interesting properties such as in food, cosmetics, medical and biological materials, not to mention fibers.[4] In particular, fibroin is approximately 370 kDa molecular mass and consists of mainly glycine, alanine, serine and tyrosine, and very few residues of sulfur amino acids,[5] which can be a strong catalyst poison of metals.

The formation of fibroin heavy metal (Cu, Cr, Zn, Ni, Sn and so on) complexes has long been studied in connection with increasing the strength, weight and luster of heavy metal absorbed silk.[6] Many of the electron-rich functional groups in the protein easily bind with the metal surface, leading to the bioconjugate. During 1956–1962,[7] Akabori and co-workers reported silk protein-supported zero-valent metal catalyst for asymmetric hydrogenation. According to their reported procedure,[7b] silk fibroin was boiled for 8 min in 0.1 N AcOH containing $PdCl_2$ and the resulting chelate was reduced under hydrogen (80 kg/cm^2) in an autoclave. Based upon Akabori's preparation method,[7] fibroin of the silk fibroin-supported palladium catalyst was most likely denatured under the drastic reaction conditions for the reason that the fibroin was exposed to the strongly acidic conditions derived from liberating HCl from $PdCl_2$ in boiling 0.1 N AcOH. This could be due to the fact that the silk palladium-catalyzed asymmetric hydrogenations are inefficient inasmuch as the reproducibility of the method was invariably poor.[7] To our best knowledge, no applicable protein-supported metal catalyst has, as yet, been reported. Quite recently, Zhou et al. reported a core-shell nano-structured gold colloid-silk fibroin bioconjugate.[8] We report herein a preparation method of a novel Pd–fibroin (Pd/Fib)

Keywords: Silk-fibroin; Hydrogenation; Palladium catalyst; Chemoselective.
* Corresponding authors. Tel.: +81 58 237 3931x225; fax: +81 58 237 5979 (H.S.); e-mail: sajiki@gifu-pu.ac.jp

0040–4020/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2004.11.080

catalyst under mild and nearly neutral reaction conditions and its application to highly chemoselective hydrogenation methods.[9]

2. Results and discussion

We chose $Pd(OAc)_2$ as a palladium source for the new Pd–fibroin catalyst (Pd/Fib) to avoid the strongly acidic conditions derived from released HCl from $PdCl_2$. The Pd absorption (1∼10 wt% of the silk fibroin) onto the silk fibroin was initiated by soaking silk fibroin [Fig. 1(a)] into a dark rust-colored MeOH solution of $Pd(OAc)_2$ [0.0235 mol/l, Fig. 1(b)] at room temperature in air. The colorless fibroin was time-dependently changed to black, which suggests the formation of zero-valent Pd. The liquid phase also changed gradually from rust to thoroughly colorless-clear [Fig. 1(c)–(e)] for 4 days, indicating the slow but complete adsorption of $Pd(OAc)_2$ on the silk fibroin and the rapid formation of the zero-valent Pd/Fib via oxidation of the silk fibroin or MeOH. Since no formation of black turbidity or silver mirror was observed during the deposition of Pd(0) onto the silk fibroin, it can be presumed that the formation of Pd(0) occurs only on the fibroin fiber. Although the preparation time of Pd/Fib could be reduced under Ar atmosphere, the preparation was carried out under atmospheric conditions from a practical standpoint. After simple filtration, the obtained Pd/Fib [Fig. 1(f)] was stable for more than three years at room temperature in air (in a capped vial) and is non-pyrophoric. The Pd/Fib can be used by cutting up the black yarn (Pd/Fib fiber) with scissors and is removed easily from the reaction mixture using a pair of tweezers or by simple filtration.

Figure 1. Preparation of Pd/Fib catalyst.

The quantitative analysis of the formation of acetic acid[10] and formaldehyde[11] was carried out to gain insight into the reduction of $Pd(OAc)_2$. For the reason that 90% of acetic acid and 70% of formaldehyde were determined from the filtered clear solution of Fig. 1(e), MeOH contributed to the reduction of $Pd(OAc)_2$ which was strongly adsorbed and coordinated by silk fibroin, while the Tyr and/or Ser residues of silk fibroin also display strong electron-donating

$$Pd(OAc)_2 \xrightarrow[MeOH,\ rt]{Fibroin} Pd(OAc)_2/Fib \xrightarrow[MeOH]{rt} Pd(0)/Fib + HCHO + 2AcOH$$

Scheme 1. Mechanism of Pd/Fib generation.

Figure 2. Silver mirror of palladium.

properties (Scheme 1). On the other hand, the formation of a silver mirror of palladium metal on the side face of the Erlenmeyer flask was observed when only the MeOH solution of $Pd(OAc)_2$ was allowed to stand in the absence of fibroin fiber at room temperature for 4 days (Fig. 2).

Scanning electron microscopy (SEM) images proved the high dispersion of amorphous palladium metal particles [Fig. 3(b)–(d)] on the smooth surface of the silk fibroin [Fig. 3(a)]. The variation of the Pd content only made a difference in the density of the Pd particles. This homogeneous dispersion was attributed to an interaction between the $Pd(OAc)_2$ and amino acids of the silk fibroin, increasing the resistance to the growth of the Pd cluster.[9]

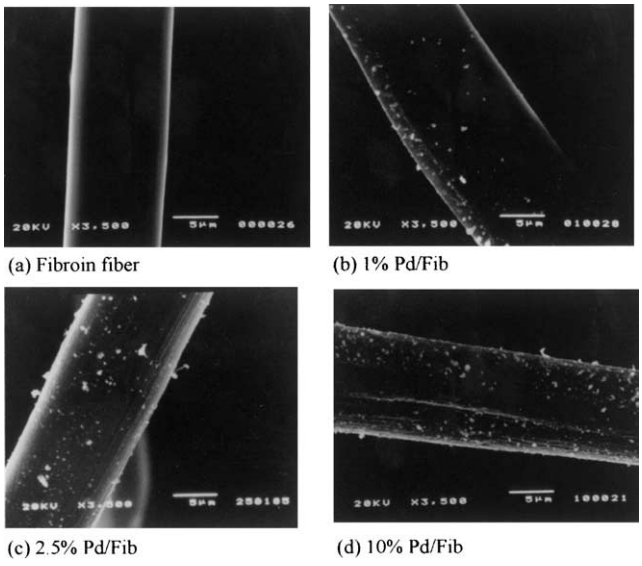
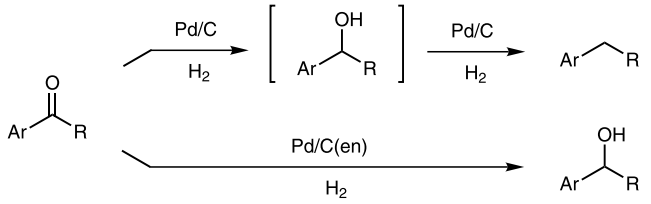


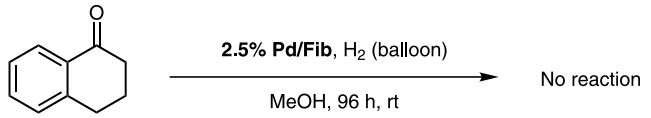
Figure 3. SEM image of original fibroin fiber (a), 1% (b), 2.5% (c) and 10% Pd/Fib (d).

It is well known that the Pd/C-catalyzed hydrogenation of aromatic carbonyls easily occurs to form methylene compounds via formation of the intermediary benzyl alcohol (Scheme 2).[1] Therefore, it is extremely difficult to achieve the chemoselective hydrogenation of olefin and acetylene functionalities leaving intact the aromatic ketone



Scheme 2. Reduction of aromatic carbonyl using Pd/C and Pd/C(en).

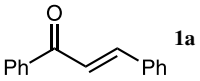
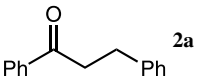
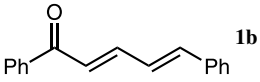
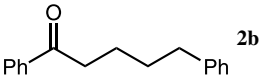
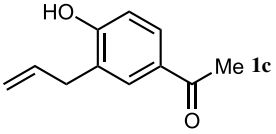
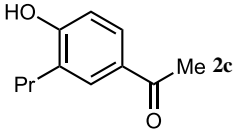
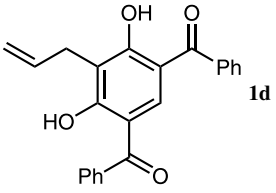
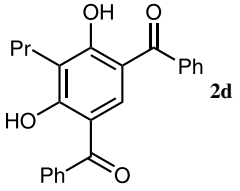
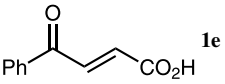
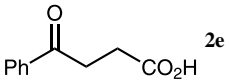
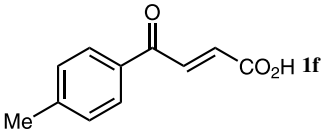
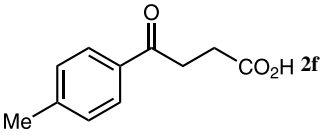
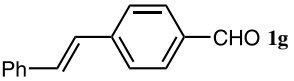
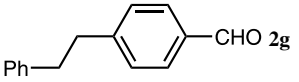
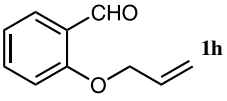
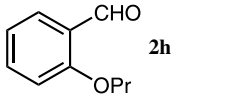
and aldehyde. Recently, we have reported a chemoselective hydrogenation method of aromatic carbonyls to form benzyl alcohols without hydrogenolysis of the intermediary benzyl alcohol using Pd/C(en) as a catalyst.[12] Following our interest in the use of Pd/Fib as a catalyst for the chemoselective hydrogenation, we found that 2.5% Pd/Fib surprisingly exhibited no catalyst activity toward the hydrogenation of aromatic carbonyl compounds (Scheme 3).



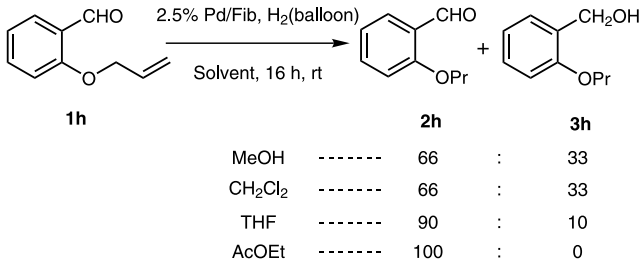
Scheme 3. Catalytic activity of 2.5% Pd/Fib toward the hydrogenation of aromatic ketone.

To explore the scope of the 2.5% Pd/Fib catalyst, the chemoselective hydrogenation of olefins in the presence of an aromatic carbonyl group within the molecule was carried out at room temperature (Table 1). Although aromatic ketones (**1a–1f**) were never reduced, hydrogenation activity of 2.5% Pd/Fib toward olefins is retained (entries 1–6). Moreover, the aromatic aldehyde (**1g**) was also stable under hydrogenation conditions using 2.5% Pd/Fib even under 5 atm pressure of hydrogen (entry 7). Although partial reduction of the aromatic aldehyde of *o*-allyloxybenzaldehyde (**1h**) was observed in MeOH, CH_2Cl_2 or THF as a solvent, the use of AcOEt as a solvent caused the perfect suppression of the reduction of the aromatic aldehyde group of **1h** (entry 8 and Scheme 4).

Table 1. Chemoselective hydrogenation of olefin in the presence of aromatic carbonyl using 2.5% Pd/Fib catalyst[a]

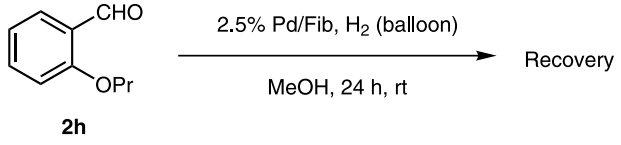
Entry	Substrate	Time (h)	Product	Yield (%)[b]
1	 **1a**	30	 **2a**	97 (99[c], 97[d])
2	 **1b**	3	 **2b**	100
3	 **1c**	37	 **2c**	99
4	 **1d**	46	 **2d**	74[e]
5	 **1e**	2	 **2e**	quant
6	 **1f**	10	 **2f**	99
7	 **1g**	24	 **2g**	100[c,e]
8	 **1h**	27	 **2h**	100[f]

[a] Unless otherwise specified, reactions were performed in 5 mL of MeOH under ambient hydrogen pressure at room temperature.
[b] Isolated yield.
[c] 5 atm pressure of hydrogen.
[d] The reaction was performed at 50 °C.
[e] 5 mL of CH_2Cl_2 was used as a solvent.
[f] 5 mL of AcOEt was used as a solvent.



Scheme 4. Solvent effect toward the hydrogenation of the aromatic aldehyde (**1h**).

While the aromatic aldehyde of **1g** was not reduced even under 5 atm pressure of hydrogen using 2.5% Pd/Fib catalyst in MeOH, the aldehyde of **1h** was partially reduced under ambient pressure of hydrogen in MeOH (entry 7 and Scheme 4). On the other hand, *o*-propyloxybenzaldehyde (**2h**) which possesses no olefin moiety was entirely recovered under the same hydrogenation conditions in MeOH (Scheme 5). According to these experimental results, the aldehyde of **1h** was partially reduced before the saturation of the olefin. Although the exact process of the partial reduction of **1h** is unclear, it has been proposed that



Scheme 5. Catalyst activity of 2.5% Pd/Fib toward the hydrogenation of aromatic aldehyde (**2h**) in MeOH.

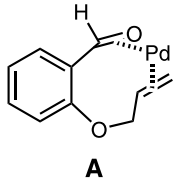


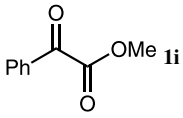
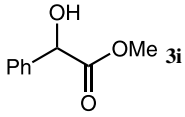
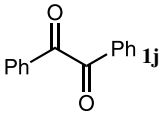
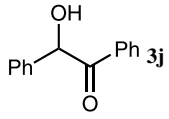
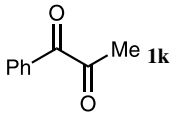
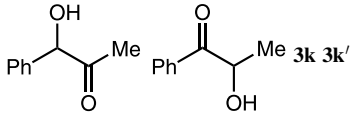
Figure 4. Cyclic coordination of **1h** with Pd (0).

the formation of a cyclic intermediate (**A**), which is obtained by the coordination of Pd metal with the olefin and aldehyde functionalities, is a key step of the competitive hydrogenation of the olefin and aldehyde of **2h** (Figure 4). Since the use of AcOEt as a solvent, which is a better ligand than the aromatic aldehyde of **2h**, should inhibit the formation of the cyclic intermediate (**A**), the selective hydrogenation was achieved in AcOEt.

While aromatic carbonyl groups were usually not reduced using 2.5% Pd/Fib (Table 1), aromatic ketones which possess ester or other ketone moieties at the α position were exceptionally reduced under the same conditions (Table 2). For example, methyl benzoylformate (**1i**), aromatic β-keto-ester, was reduced to the corresponding alcohol (**3i**). Regrettably, stereoselectivity of **3i** was extremely poor (only 4% ee). Benzil (**1j**) and 1-phenylpropane-1,3-dione (**1k**) which are aromatic 1,2-diketone were also reduced to the corresponding α-hydroxyketones. Again, we expected the formation of the neighboring-carbonyl group related cyclic palladium coordinated intermediate to be a key step of the exceptional reduction of the carbonyl group.

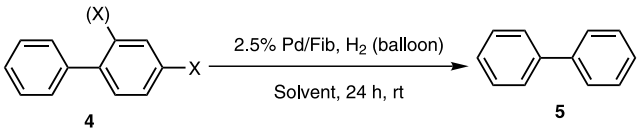
It is well known that aromatic chlorides are much less reactive than aromatic bromides and iodides toward the hydrogenation conditions and, hence, the dechlorination of aromatic chloride cannot readily be achieved and the hydrodechlorination reactions are very frequently incomplete but proceeded.[13] Needless to say, Pd/C(en)[2] or commercial Pd/C[1]-catalyzed chemoselective hydrogenation with retention of aromatic halides could not be accomplished,[13] whereas aromatic halides entirely tolerate the hydrogenation using 2.5% Pd/Fib (Table 3). Although partial hydrogenolysis of 4-chlorobiphenyl (**4b**) and 4-bromobiphenyl (**4c**) was observed in MeOH (entries 2 and 4), the use of THF as a solvent perfectly suppressed the partial hydrogenolysis (entries 3 and 5). 4-Fluorobiphenyl (**4a**) and 2-iodobiphenyl (**4d**) were stable under the hydrogenation conditions in MeOH.

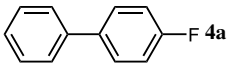
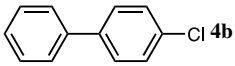
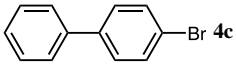
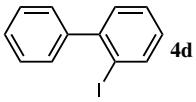
Table 2. Reducible aromatic carbonyls under the hydrogenation conditions using 2.5% Pd/Fib[a]

Entry	Substrate	Time (h)	Product	Yield (%)[b]
1	 **1i**	8	 **3i**	98
2	 **1j**	46	 **3j**	98[c]
3	 **1k**	43	 **3k** **3k′** (85 : 15)[e]	—[d]

[a] Unless otherwise specified, reactions were performed in 5 mL of MeOH under hydrogenation conditions at room temperature.
[b] Isolated yield.
[c] Under 5 atm pressure of hydrogen.
[d] Under 10 atm pressure of hydrogen.
[e] Determined by ^{1}H NMR (starting material was disappeared).

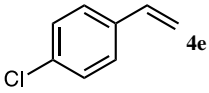
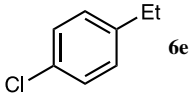
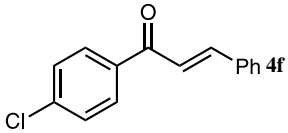
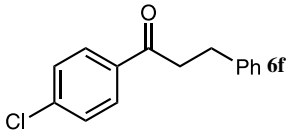
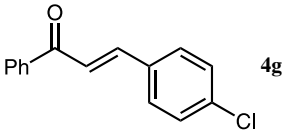
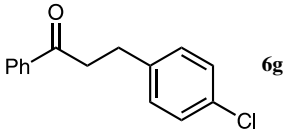
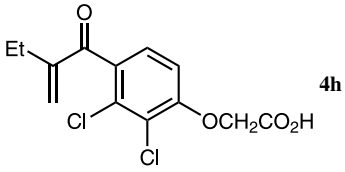
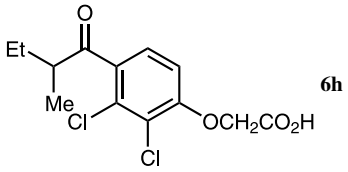
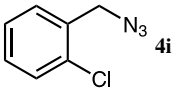
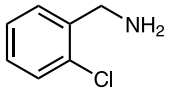
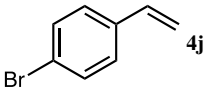
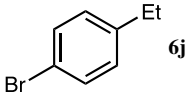
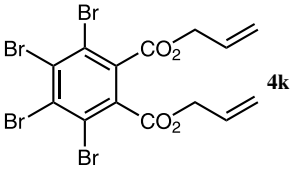
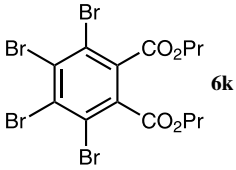
Table 3. Catalytic activity of 2.5% Pd/Fib toward the hydrogenolysis of aromatic halides



Entry	Substrate	Solvent	**4**:**5**[a]	Recovery (%)
1	 **4a**	MeOH	100:0	95
2	 **4b**	MeOH	95:5	—
3		THF	100:0	99
4	 **4c**	MeOH	84:16	—
5		THF	100:0	91
6	 **4d**	MeOH	100:0	98

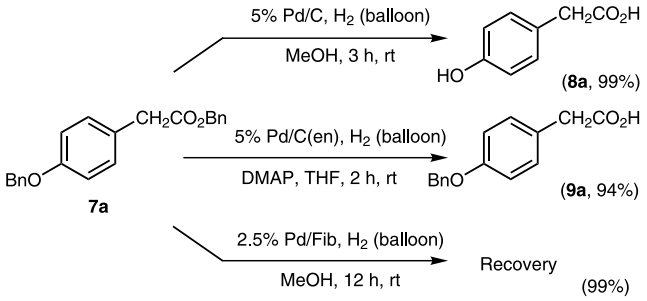
[a] Determined by ^{1}H NMR.

Table 4. Chemoselective hydrogenation of olefin and azide in the presence of aromatic halide using 2.5% Pd/Fib catalyst[a]

Entry	Substrate	Time (h)	Product	Yield (%)[b]
1	 **4e**	24	 **6e**	100[c]
2	 **4f**	20	 **6f**	98
3	 **4g**	21	 **6g**	99[d]
4	 **4h**	12	 **6h**	100
5	 **4i**	24	 **6i**	91
6	 **4j**	24	 **6j**	100[c]
7	 **4k**	3	 **6k**	94

[a] Unless otherwise specified, reactions were performed in 5 mL of MeOH under ambient hydrogen atmosphere at room temperature.
[b] Isolated yield.
[c] Performed in CD_3OD as a solvent and determined by ^{1}H NMR.
[d] Performed in 15 mL of MeOH.

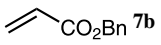
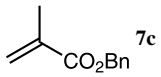
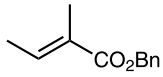
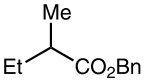
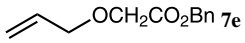
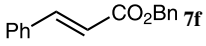
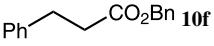
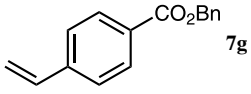
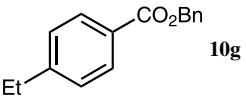
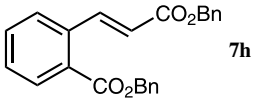
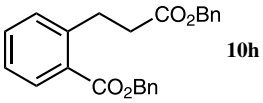
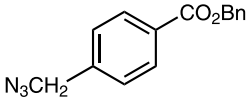
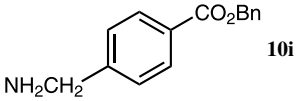
Consequently, the chemoselective hydrogenation of a variety of substrates containing aromatic halides and olefin or azide functions within a molecule was carried out at room temperature (Table 4). First, 4-chloro and 4-bromo styrenes (**4e** and **4j**) were hydrogenated using 2.5% Pd/Fib in CD_3OD because of the low boiling point of the products. Not only chloride but also bromide was never cleaved while the olefin was chemoselectively hydrogenated (entries 1 and 6). In addition, only the olefin moiety in compounds **4f–4h** containing aromatic chloride and ketone was selectively hydrogenated, to give the corresponding saturated compounds **6f–6h** (entries 2–4). The azide group of **4i** was also hydrogenated to the corresponding amine (**6i**) (entry 5). Furthermore, 2.5% Pd/Fib did not catalyze the hydrogenolysis of even multi-brominated aromatic bromide (**4k**) and the chemoselective hydrogenation of the olefins was achieved (entry 7). According to these results, 2.5% Pd/Fib catalyst is obviously applicable to the chemoselective hydrogenation of olefin and azide functions distinguishing the aromatic halides.



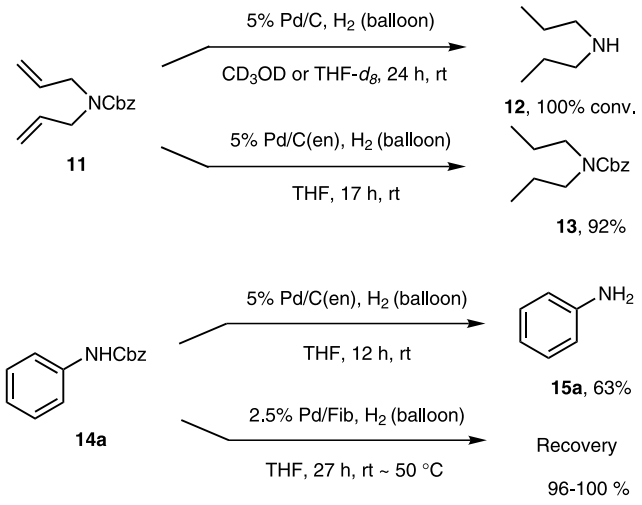
Scheme 6. Catalytic activity of Pd catalysts toward the hydrogenation of benzyl ether and ester.

Despite numerous literature precedents, chemoselective reduction of reducible functionalities such as alkynes, alkenes and azides remains a challenge in organic synthesis.[1] Especially, while benzyl ester or *N*-Cbz protective groups are widely used in organic synthesis, they are labile under hydrogenation conditions, and it is extremely difficult to keep such groups intact during a synthetic process involving hydrogenation steps.[14] In order to solve this problem, Misiti et al. have reported 3% Pd/C-catalyzed selective hydrogenation of a di-substituted olefin of γ-amino-α,β-unsaturated (conjugate) esters in the presence of a benzyl ester or *N*-Cbz protective group.[15] However, the method has limitation with regard to generality, and the stability of the benzyl esters and *N*-Cbz groups under the conditions was time-dependent.[15,16] During our efforts to extend the applicability of the Pd/Fib catalyst, we found that Pd/Fib indicates almost no catalytic activity towards the hydrogenolysis of benzyl ether and benzyl ester compared with Pd/C and Pd/C(en)[2a] (Scheme 6). The hydrogenolysis of 4-benzyloxyphenylacetic acid benzyl ester (**7a**) catalyzed by 2.5% Pd/Fib resulted in no reaction even after 12 h under ordinary hydrogen pressure (recovery of the starting material **7a** in 99%). On the other hand, the use of 5% Pd/C (Aldrich)[1] as a catalyst resulted in the hydrogenolysis of both the benzyl ether and the benzyl ester of **7a** to give the corresponding 4-hydroxyphenylacetic acid (**8a**) in 99% isolated yield. 5% Pd/C(en) catalyzed

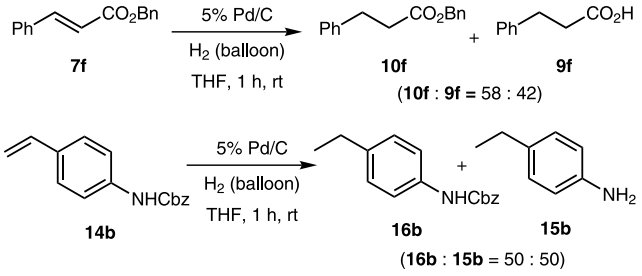
Table 5. Chemoselective hydrogenation of olefin and azide functionalities in the presence of a benzyl ester using 2.5% Pd/Fib catalyst[a]

1	Substrate	Solvent	Time (h)	Product	Yield (%)[b]
1	 **7b**	THF-d_8	7	$EtCO_2Bn$ **10b**	91[c]
2	 **7c**	THF-d_8	7	$iPrCO_2Bn$ **10c**	93[c]
3	 **7d**	MeOH	18	 **10d**	77[d]
4	 **7e**	MeOH	8	$PrOCH_2CO_2Bn$ **10e**	99
5	 **7f**	THF	24	 **10f**	98
6	 **7g**	MeOH	6	 **10g**	97
7	 **7h**	MeOH	12	 **10h**	100 (100)[e]
8	 **7i**	MeOH	17	 **10i**	100

[a] Unless otherwise specified, reactions were performed in 5 mL of the solvent under ambient hydrogen pressure at room temperature.
[b] Isolated yield.
[c] Performed in THF-d_8 (0.75 mL) and determined by ^1H NMR.
[d] Under 5 atm pressure of hydrogen.
[e] The reaction was performed at 50 °C.



Scheme 7. Catalytic activity of Pd catalysts toward the *N*-Cbz group of aliphatic and aromatic amines.



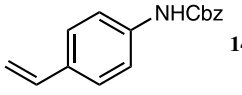
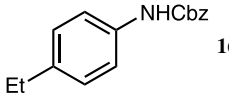
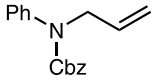
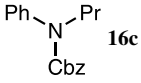
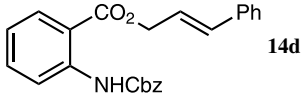
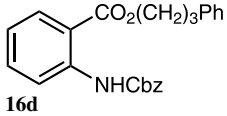
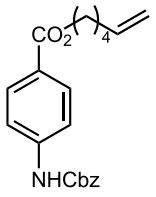
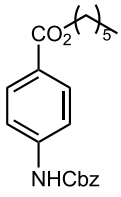
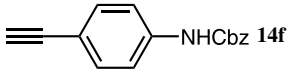
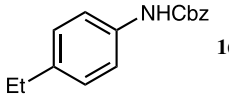
Scheme 8. Hydrogenation of **7f** and **14b** using commercial 5% Pd/C catalyst.

chemoselective hydrogenation of only the benzyl ester of **7a** with retention of the benzyl ether to give the corresponding 4-benzyloxyphenylacetic acid (**9a**) in 94% isolated yield.[2a] Judging from these results so far obtained, we are now in a position to disclose that the Pd/Fib catalyst is very efficient for chemoselective hydrogenation with retention of the benzyl ester within a molecule.

To explore the scope of the 2.5% Pd/Fib catalyst, the hydrogenation of a number of substrates containing a benzyl ester was investigated (Table 5). The terminal and internal olefin and azide functionalities were selectively reduced in the presence of α,β-unsaturated (conjugated) benzyl esters (**7b**–**7d**, **7f** and **7h**) (entries 1–3, 5 and 7), a non-conjugated benzyl ester (**7e**) (entry 4) and benzoic acid benzyl ester derivatives (**7g**, **7h** and **7i**) (entries 6, 7 and 8). A feature of the hydrogenation of benzyl ester derivatives is that the catalyst activity of Pd/Fib toward the benzyl esters is strongly influenced by the solvent. The benzyl esters of substrates **7b**, **7c** and **7f** were partially or completely hydrogenolized in MeOH as a solvent. However, no hydrogenolysis of the benzyl ester was observed in THF as a solvent as can be seen from entries 1, 2 and 5. On occasions when the partial hydrogenolysis of the benzyl ester of the substrate occurred in MeOH, the use of THF as a solvent gave satisfactory results (entries 1, 2 and 5).[2a,b,17,18]

N-Cbz (carbobenzoxy) protective groups are easily deprotected under hydrogenation conditions using Pd/C as a catalyst.[19] Recently, we reported the Pd/C(en) catalyzed-chemoselective hydrogenation with retention of the *N*-Cbz protective group of aliphatic amines although the chemoselective hydrogenation with retention of the aromatic

Table 6. Chemoselective hydrogenation of olefin and acetylene in the presence of aromatic *N*-Cbz group using 2.5% Pd/Fib catalyst[a]

Entry	Substrate	Solvent	Time (h)	Product	Yield (%)[b]
1	 **14b**	THF	5	 **16b**	92
2	 **14c**	MeOH	48	 **16c**	97
3	 **14d**	THF	34	 **16d**	99[c]
4	 **14e**	MeOH	22	 **16e**	100
5	 **14f**	MeOH	32	 **16f**	92[d]

[a] Unless otherwise specified, reactions were performed in 5 mL of the solvent under ambient hydrogen pressure at room temperature.
[b] Isolated yield.
[c] Under 10 atm pressure of hydrogen.
[d] Under 3 atm pressure of hydrogen.

N-Cbz groups or benzyl esters could not be accomplished.[2a,17,20] Although the hydrogenation of the substrate (**11**) containing an *N*-Cbz group of aliphatic amine and olefin functionalities within a molecule catalyzed by 5% Pd/C gave totally saturated and simultaneously deprotected product **12** as the sole product, the use of 5% Pd/C(en) catalyst in THF resulted in entirely chemoselective hydrogenation and the *N*-Cbz protective group was tolerated under the reaction conditions (Scheme 7). However, the *N*-Cbz protective group of an aromatic amine is easily deprotected under the same reaction conditions,[2a,17] for instance, the *N*-Cbz protective group of aniline (**14a**) was smoothly deprotected under the hydrogenation conditions using Pd/C(en) in THF.[2a,17] During our efforts to overcome this problem, we found that 2.5% Pd/Fib possesses no catalyst activity toward the hydrogenolysis of the aromatic *N*-Cbz group (**14a**) (Scheme 7).

The catalyst activity of 2.5% Pd/Fib toward reducible functionalities is much lower than the catalyst activity of Pd/C and Pd/C(en). The olefins of **7f** and **14b** were completely hydrogenated within an hour together with the partial hydrogenolysis of benzyl ester and *N*-Cbz, respectively (Scheme 8) with commercial 5% Pd/C as a catalyst, while the complete hydrogenation of the olefins required much longer time with Pd/Fib (24 and 5 h, respectively; Table 5, entry 5 and Table 6, entry 1). Therefore, some sterically hindered olefins such as **7d** (Table 5, entry 3), **14d** (Table 6, entry 3), *trans*-stilben (**17**) and some cinnamate type compounds (**18** and **19**) were irreducible under ambient pressure of hydrogen using the 2.5% Pd/Fib (Figure 5) with exceptional result (e.g. Table 5, entries 5 and 7). In addition, a competitive experiment using *cis*-Jasmone (**20**) which has a di-substituted *cis*-olefin and a tetra-substituted olefin as a substrate indicated that only the *cis*-olefin was chemoselectively reduced to the corresponding dihydrojasmone (**21**). Consequently, the hydrogenation using 2.5% Pd/Fib can distinguish between hindered and unhindered olefins and the chemoselective hydrogenation of unhindered olefin was efficiently achieved (Scheme 9).

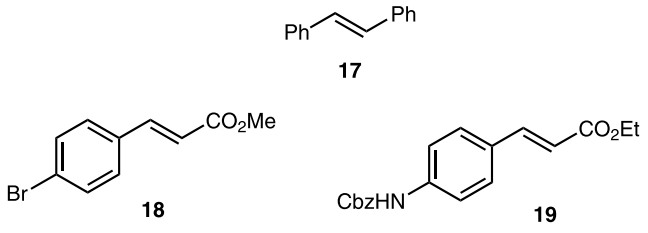
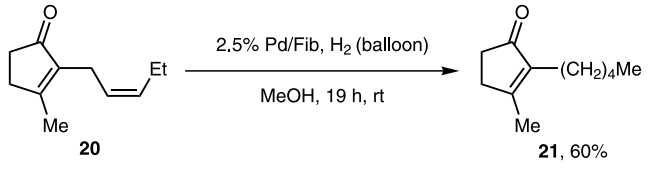


Figure 5. Irreducible olefins under ambient pressure of hydrogen using 2.5% Pd/Fib in MeOH.



Scheme 9. Chemoselective hydrogenation between two different olefins.

The chemoselectivity of the hydrogenation could be attributable to the catalyst poison effect of the coordinated silk fibroin support toward the zero valent palladium metal and the significant decrease in the active surface area of palladium metal by the formation of a minute cluster (Figure 3). In the Pd/Fib catalyst, the original affinity of palladium to aromatic carbonyls, halides, benzyl esters and *N*-Cbz protective groups was drastically and selectively reduced by fibroin.

3. Conclusion

Silk-fibroin supported palladium catalyst (Pd/Fib) was prepared by incipient wetness impregnation with a rust-colored MeOH solution of $Pd(OAc)_2$. After the palladium (II) was absorbed completely in the fibroin, the zero-valent Pd was formed on the fibroin fiber via oxidation by MeOH as a reductant. The Pd/Fib catalyst, black-colored yarn, shows chemoselectivity in hydrogenation of acetylene, olefin and azide functionalities in the presence of aromatic ketone, aldehyde and halide, benzyl ester and aromatic *N*-Cbz protective groups. These novel chemoselective hydrogenation methods using Pd/Fib should contribute to broad organic synthetic chemistry fields.

4. Experimental

4.1. General

^1H and ^{13}C NMR spectra were recorded on a JEOL AL 400 spectrometer, JEOL EX 400 spectrometer, or a JEOL GL 270 spectrometer with tetramethylsilane or residual protiated solvent used as a reference. Elemental analyses were performed by YANACO CHN CORDER MT-5 instrument. EI and FAB Mass spectra were taken on a JEOL JMS-SX102A instrument. SEM (Scanning Electron Microscopy) image were taken on a JEOL JSM-T330A. Flash column chromatography was performed with silica gel Merck 60 (230–400 mesh ASTM) according to the method of Still.[21] MeOH for HPLC and AcOEt dehydrated were purchased from Wako Pure Chemical Industries, Ltd. and used without purification. THF was distilled from sodium benzophenone ketyl. CH_2Cl_2 was distilled from calcium hydride. All other reagents were purchased from commercial sources and used without further purification.

4.1.1. Preparation of silk fibroin. Raw silk of *Bombyx mori* (10.0 g) wrapped in gauze was soaked in an aqueous solution (1.00 L) of Na_2CO_3 (500 mg, 6.02 mmol), $Na_2S_2O_4$ (100 mg, 0.57 mmol) and ethylenediaminetetraacetic acid dipotassium salt dihydrate (400 mg, 0.99 mmol) and boiled for an hour. The resulting silk was washed vigorously with water and dried in the shade to afford silk fibroin (7.83 g. Anal. Found: C, 47.57; H, 6.38; N, 18.37: sample 1.779 mg: ash 0.02 mg).

4.1.2. Preparation of 2.5% Pd/Fib. To a rust-colored solution of palladium acetate (1.06 g, 4.72 mmol) in MeOH (200 mL) at room temperature was soaked silk fibroin (20.0 g) for 4 days. The silk fiber changed gradually from white to black and the solution also changed gradually from rust to thoroughly colorless-clear. The resulting black fiber was filtered, washed vigorously with MeOH (500 mL), and

dried under reduced pressure to give the 2.5% Pd/Fib. [1] Anal. Found: C. 45.25; H, 5.99; N, 16.97: sample 1.92 mg: ash 0.01 mg. [2] Anal. Found: C. 46.56; H, 6.18; N, 17.95: sample 1.704 mg: ash 0.07 mg. [3] Anal. Found: C. 46.76; H, 6.25; N, 18.05: sample 1.766 mg: ash 0.04 mg.

4.1.3. Quantitative analysis of aldehyde.[10] To a solution of palladium acetate (52.7 mg, 0.23 mmol) in MeOH (10.0 mL) under Ar atmosphere at room temperature was soaked silk fibroin (1.00 g) for 4 days. The filtrate was diluted 200 times with distilled water. A mixture of the sample solution (5.00 mL) and acetylacetone solution (5.00 mL) which was prepared by distilled ammonium acetate (15.0 g), acetic acid (0.30 mL) and acetylacetone (0.20 mL) to the 100 mL with water was heated on a hot water bath for 10 min. The absorbance was determined by 254 nm. Calibration curve of formaldehyde was obtained by plotting peak size on the *y*-axis versus sample concentration on the *x*-axis for a series of samples with known concentrations using the data for the 1.25, 2.50 and 5.00 μg/mL standard solutions of formaldehyde.

4.1.4. Quantitative analysis of acetic acid.[11] To a solution of palladium acetate (52.7 mg, 0.23 mmol) in MeOH (10.0 mL) under Ar atmosphere at room temperature was soaked silk fibroin (1.00 g) for 4 days. The filtrate was diluted 10 times with distilled water. The solution was titrated with 0.01 N NaOH solution in the presence of phenolphthalein which was standardized by potassium hydrogen phthalate solution.

4.1.5. Formation of silver mirror of palladium. The MeOH (10.0 mL) solution of palladium acetate (52.7 mg, 0.23 mmol) was allowed to stand in the absence of fibroin fiber under Ar atmosphere at room temperature for 4 days. The formation of a silver mirror of palladium metal on the side face of the Erlenmeyer flask was observed.

4.1.6. Preparation of 1, 5 and 10% Pd/Fib. Silk fibroin (1.00 g) was soaked in a rust-colored solution of palladium acetate (1%: 21.2 mg, 5%: 106 mg, 10%: 211 mg) in MeOH (30.0 mL) at room temperature for 4 days. The resulting black fiber was filtered, washed vigorously with MeOH (100 mL), and dried under reduced pressure to give the 1% Pd/Fib. Anal. Found: C. 47.11; H, 6.18; N, 18.20: sample 2.309 mg: ash 0.08 mg. 5% Pd/Fib Anal. Found: C. 45.79; H, 6.02; N, 17.59: sample 1.934 mg: ash 0.09 mg. 10% Pd/Fib Anal. Found: C, 45.93; H, 6.04; N, 17.83: sample 1.797 mg: ash 0.13 mg.

4.1.7. Synthesis of substrate.

4.1.7.1. 2-Chlorobenzylazide (4i). To a solution of 2-chlorobenzylchloride (1.61 g, 10.0 mmol) in DMF (10.0 mL) at room temperature was added sodium azide (1.95 g, 30.0 mmol). The solution was stirred at room temperature for 48 h, after which time the solvent was removed under vacuum pressure. The residue was extracted with ethyl acetate (100 mL) and water (100 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford 2-chlorobenzylazide (**4i**) as a colorless oil (1.03 g, 62%). ^{1}H NMR ($CDCl_3$): δ=7.29–7.43 (m, 4H), 4.26 (s, 2H); ^{13}C NMR ($CDCl_3$): δ=133.8, 133.3, 130.0, 129.8, 129.6, 127.1, 52.3; MS (EI) *m*/*z* 167 (M^+, 38%), 140 (35%), 138 (99%), 127 (34%), 125 (100%), 111 (35%), 102 (36%), 89 (29%), 77 (56%), 75 (45%), 51 (37%), 50 (42%); HRMS (EI) Calcd for $C_{10}H_{12}O_2$ (M^+): 167.0250. Found: 167.0245.

4.1.7.2. Benzyl 4-benzyloxyphenylacetate (7a).[2a] To a solution of 4-benzyloxyphenylacetic acid (2.42 g, 10.0 mmol) and Et_3N (1.40 mL, 10.0 mmol) in THF (20.0 mL) at room temperature was added benzyl bromide (1.19 mL, 10.0 mmol). The solution was stirred at room temperature for 24 h, after which time the solvent was removed under vacuum pressure. The residue was extracted with ether (100 mL) and water (100 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was applied to flash silica gel column chromatography to afford benzyl 4-benzyloxyphenylacetate (**7a**) as a colorless solid (2.19 g, 88%). ^{1}H NMR ($CDCl_3$): δ=7.30–7.49 (m, 10H), 7.20 (d, *J*=8.8 Hz, 2H), 6.93 (d, *J*=8.8 Hz, 2H), 5.12 (s, 3H), 5.05 (s, 3H), 3.60 (s, 3H); ^{13}C NMR ($CDCl_3$): δ=173.6, 159.8, 138.8, 138.8, 137.7, 132.3, 132.2, 130.4, 130.0, 130.0, 129.8, 129.3, 71.8, 68.4, 42.3; MS (EI) *m*/*z* 332 (M^+,), 242, 149, 91 (100%). Anal. Calcd for $C_{22}H_{20}O_3$: C, 79.49; H, 6.06. Found: C, 79.21; H, 6.10.

4.1.7.3. Benzyl allyloxyacetate (7e). To a solution of benzyl glycolate (0.83 g, 5.00 mmol) and NaH (240 mg, 6.00 mmol) in DMF (10.0 mL) was added allyl bromide (0.43 mL, 5.00 mmol). The solution was refluxed for 21 h, after which time the solvent was removed under vacuum pressure. The residue was extracted with ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was applied to flash silica gel column chromatography (hexane/ether=20:1) to afford benzyl allyloxyacetate (**7e**) as a pale yellow oil (499 mg, 48%). ^{1}H NMR ($CDCl_3$): δ=7.37–7.33 (m, 5H), 5.96–5.86 (m, 1H), 5.29 and 5.23 (each d, *J*=171.1, 10.8 Hz, each 1H), 5.20 (s, 2H), 4.13 (s, 2H), 4.10 (d, *J*=5.9 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ=170.2, 135.4, 133.7, 128.6, 128.4, 127.6, 127.0, 118.2, 72.4, 67.1, 66.5; MS (FAB: Gly) *m*/*z* 207 (M^++H, 9%), 149 (7%), 131 (5%); HRMS (FAB: Gly) Calcd for $C_{11}H_{15}O_3$ (M^++H): 207.1021. Found: 207.1025.

4.1.7.4. Benzyl 4-vinylbenzoate (7g). To a solution of 4-vinylbenzoic acid (0.74 g, 5.00 mmol), EDC·HCl (1.15 g, 6.00 mmol) and DMAP (61.1 mg, 0.50 mmol) in CH_2Cl_2 (15.0 mL) was added benzyl alcohol (541 mg, 5.00 mmol). After the solution was refluxed for 1 h, the mixture was extracted with chloroform (50 mL×2) and water (50 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was applied to flash silica gel column chromatography (hexane/ether=100:1) to afford benzyl 4-vinylbenzoate (**7g**) as a pale yellow oil (0.93 g, 78%). ^{1}H NMR ($CDCl_3$): δ=8.03 (d, *J*=8.3 Hz, 2H), 7.47–7.34 (m, 7H), 6.75 (dd, *J*=10.7, 17.6 Hz, 1H), 5.86 and 5.38 (each d, *J*=17.6 Hz, each 1H), 5.36 (s, 2H); ^{13}C NMR ($CDCl_3$): δ=116.2, 142.1, 136.1, 136.0, 130.0, 129.3, 128.6, 128.2, 128.2, 126.1, 116.5, 66.7; MS (EI) *m*/*z* 238 (M^+, 40%), 131

(100%), 91 (46%), 77 (15%); HRMS (EI) Calcd for $C_{16}H_{14}O_2$ (M^+): 238.0994. Found: 238.0985.

4.1.7.5. Benzyl 2-(benzyloxycarbonyl)cinnamate (7h). To a solution of 2-carboxycinnamic acid (0.96 g, 5.00 mmol), EDC·HCl (2.30 g, 12.0 mmol) and DMAP (112 mg, 1.00 mmol) in CH_2Cl_2 (10.0 mL) was added benzyl alcohol (1.08 g, 10.0 mmol). The solution was stirred at room temperature for 48 h, after which time the solvent was removed under vacuum pressure. The residue was extracted with ethyl acetate (100 mL) and water (100 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was applied to flash silica gel column chromatography (hexane/ether=20:1) to afford benzyl 2-(benzyloxycarbonyl)cinnamate (**7h**) as a colorless oil (958 mg, 51%). ^{1}H NMR ($CDCl_3$): δ=8.52 (d, J=15.6 Hz, 1H), 7.99 (d, J=7.8 Hz, 1H), 7.33–7.59 (m, 13H), 6.34 (d, J=15.6 Hz, 1H), 5.36 (s, 2H), 5.26 (s, 2H); ^{13}C NMR ($CDCL_3$): δ= 166.5, 166.2, 144.4, 136.5, 136.1, 135.6, 132.4, 130.9, 130.0, 129.4, 128.6, 128.4, 128.4, 128.2, 128.0, 120.8, 67.2, 66.3; MS (EI) *m/z* 372 (M^+, 5%), 28 (100%), 91 (100%), 105 (12%), 77 (10%), 44 (10%); HRMS (EI) Calcd for $C_{24}H_{20}O_4$ (M^+): 372.1364. Found: 372.13615.

4.1.7.6. Benzyl 4-azidomethylbenzoate (7i). To a solution of 4-hydroxymethylbenzoic acid (1.52 g, 10.0 mmol), Et_3N (1.70 mL, 12.0 mmol) in CH_2Cl_2 (10.0 mL) was added benzyl bromide (1.20 mL, 10.0 mmol). After the solution was stirred at room temperature for 23 h, the mixture was extracted with chloroform (100 mL) and water (100 mL). The organic layer was washed with sat. $NaHCO_3$ solution (100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was applied to flash silica gel column chromatography (hexane/ether=2:1) to afford benzyl 4-hydroxymethylbenzoate[22] as a colorless solid (1.14 g, 47%). ^{1}H NMR ($CDCl_3$): δ=8.07 (d, J=8.3 Hz, 2H), 7.46–7.32 (m, 7H), 5.37 (s, 2H), 4.77 (d, J=5.9 Hz, 2H), 1.77 (t, J=5.9 Hz, OH). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.47; H, 5.92.

To a solution of benzyl 4-hydroxymethylbenzoate (0.30 g, 1.24 mmol) in CCl_4 (10.0 mL) was added Ph_3P (0.52 g, 2.00 mmol). The solution was refluxed for 18 h, after which time the solvent was removed under vacuum pressure. The residue was applied to a flash silica gel column chromatography (hexane/ether=50:1) to afford benzyl 4-chloromethylbenzoate[23] (0.26 g, 82%). ^{1}H NMR ($CDCl_3$): δ= 8.07 (d, J=8.3 Hz, 2H), 7.46–7.32 (m, 7H), 5.37 (s, 2H), 4.60 (s, 2H); MS (EI) *m/z* 262 (M^++2, 10%), 260 (M^+, 33%), 155 (32%), 153 (100%), 91 (64%).

To a solution of benzyl 4-chloromethylbenzoate (0.26 g, 0.96 mmol) in DMF (10.0 mL) was added NaN_3 (0.20 g, 3.00 mmol). The solution was stirred at room temperature for 12 h, after which time the solvent was removed under vacuum pressure. The residue was extracted with ethyl acetate (100 mL) and water (100 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford benzyl 4-azidomethylbenzoate (**7i**) as a pale yellow oil (0.26 g, 98%). ^{1}H NMR ($CDCl_3$): δ=8.10 (d, J=7.8 Hz, 2H), 7.47–7.35 (m, 7H), 5.38 (s, 2H), 4.42 (s, 2H); ^{13}C NMR ($CDCl_3$): δ=165.9, 140.5, 135.9, 130.2, 130.1, 128.6, 128.3, 128.2, 127.9, 66.8, 54.3; MS (EI) *m/z* 267 (M^+, 28%), 239 (50%), 160 (40%), 132 (96%), 91 (100%), 77 (35%); HRMS (EI) Calcd for $C_{15}H_{13}N_3O_2$ (M^+): 267.1008. Found: 267.1000.

4.1.7.7. *N*-(Benzyloxycarbonyl)diallylamine (11).[17] To a solution of diallylamine (1.94 g, 20.0 mmol) in CH_2Cl_2 (10.0 mL) was added *N*-(benzyloxycarbonyloxy)succinimide (5.48 g, 22.0 mmol). The solution was stirred at room temperature for 7 h, after which time the solvent was removed under vacuum pressure. The residue was extracted with ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with water (30 mL), sat. $NaHCO_3$ solution (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford *N*-(benzyloxycarbonyl)diallylamine (**11**) as a yellow oil (2.52 g, 55%). ^{1}H NMR ($CDCl_3$): δ=7.30–7.36 (m, 5H), 5.70–5.83 (m, 2H), 5.15 (s, 2H), 5.05–5.19 (m, 2H), 3.87–3.90 (m, 2H); HRMS (EI) Calcd for $C_{14}H_{18}NO_2$ (M^+): 232.1337. Found: 232.1346.

4.1.7.8. *N*-(Benzyloxycarbonyl)aniline (14a).[24] To a solution of aniline (0.46 g, 5.00 mmol) in THF (10.0 mL) was added *N*-(benzyloxycarbonyloxy)succinimide (1.45 g, 6.00 mmol). After the solution was stirred at room temperature for 20 h, the mixture was extracted with ethyl acetate (150 mL) and water (100 mL×2). The organic layer was washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was applied to flash silica gel column chromatography (hexane/ether=20:1) to afford *N*-(benzyloxycarbonyl)aniline (**14a**) as a colorless solid (1.08 g, 95%). ^{1}H NMR ($CDCl_3$): δ= 7.65–7.25 (m, 1H), 7.06 (t, J=7.3 Hz, 1H), 6.72 (brs, NH), 5.20 (s, 2H). Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.98; H, 5.61; N, 6.13.

4.1.7.9. *N*-Benzyloxycarbonyl-4-vinylaniline (14b).[17] To a solution of 4-vinylaniline (1.00 g, 8.39 mmol) in CH_2Cl_2 (10.0 mL) was added *N*-(benzyloxycarbonyloxy)-succinimide (2.45 g, 10.1 mmol). The solution was stirred at room temperature for 7 h, after which time the solvent was removed under vacuum pressure. The residue was extracted with ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with water (30 mL), sat. $NaHCO_3$ solution (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford *N*-benzyloxycarbonyl-4-vinylaniline (**14b**) as a pale yellow solid (1.99 g, 92%). ^{1}H NMR ($CDCl_3$): δ=7.35–7.40 (m, 9H), 6.67 (dd, J=10.8, 17.6 Hz, 2H), 5.66 (d, J=17.6 Hz, 1H), 5.20 (s, 2H). Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.79; H, 5.99; N, 5.54.

4.1.7.10. *N*-Allyl-*N*-(benzyloxycarbonyl)aniline (14c).[17] To a solution of *N*-allylaniline (1.33 g, 10.0 mmol) in CH_2Cl_2 (10.0 mL) was added *N*-(benzyloxycarbonyloxy)-succinimide (2.91 g, 12.0 mmol). The solution was stirred at room temperature for 7 h, after which time the solvent was removed under vacuum pressure. The residue was extracted with ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with water (30 mL), sat. $NaHCO_3$ solution (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford

N-allyl-*N*-(benzyloxycarbonyl)aniline (**14c**) as a yellow oil (2.28 g, 85%). ^{1}H NMR ($CDCl_3$): δ=7.19–7.40 (m, 10H), 5.86–5.98 (m, 1H), 5.16 (s, 2H), 5.10–5.20 (m, 2H), 4.26–4.29 (m, 2H); HRMS (EI) Calcd for $C_{17}H_{17}NO_2$ (M^+): 267.1259. Found: 267.1250.

4.1.7.11. Cinnamyl *N*-(benzyloxycarbonyl)anthranilate (14d). To a solution of cinnamyl anthranilate (1.20 g, 5.00 mmol) and NaH (60% dispersion in mineral oil, 0.36 g, 9.00 mmol) in THF (20.0 mL) was added benzyl chloroformate (1.29 g, 9.00 mmol). After the solution was stirred at room temperature for 46 h, the mixture was extracted with ethyl acetate (100 mL) and phosphate buffer (100 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was applied to flash silica gel column chromatography (hexane/ether=20:1) to afford cinnamyl *N*-(benzyloxycarbonyl)anthranilate (**14d**) as a colorless solid (1.15 g, 59%); mp 72–72.5 °C. ^{1}H NMR ($CDCl_3$): δ=10.59 (s, NH), 8.47 (d, J=7.8 Hz, 1H), 8.47 (d, J=7.8 Hz, 1H), 8.07 (d, J=7.8 Hz, 1H), 7.54 (t, J=7.8 Hz, 1H), 7.44–7.25 (m, 5H), 7.04 (t, J=7.8 Hz, 1H), 6.74 (d, J=15.9 Hz, 1H), 6.38 (dt, J=15.9, 6.3 Hz, 1H), 5.22 (s, 2H), 4.96 (d, J=6.3 Hz, 2H). Anal. Calcd for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.46; N, 3.62. Found: C, 74.42; H, 5.52; N, 3.66.

4.1.7.12. 5′-Hexenyl 4-(benzyloxycarbonylamino)-benzoate (14e). To a solution of 4-aminobenzoic acid (1.37 g, 10.0 mmol) in THF (10.0 mL) was added *N*-(benzyloxycarbonyloxy)succinimide (2.91 g, 12.0 mmol). The solution was stirred at room temperature for 48 h, after which time the solvent was removed under vacuum pressure. The residue was extracted with ethyl acetate (100 mL) and water (100 mL×2). The organic layer was washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was applied to flash silica gel column chromatography (chloroform/methanol=100:1) to afford 4-(benzyloxycarbonylamino)benzoic acid[25] as a fresh-colored solid (crude) (2.21 g, 81%). ^{1}H NMR (CD_3OD): δ=7.93 (d, J=8.8 Hz, 2H), 7.54 (d, J=8.8 Hz, 2H), 7.42–7.30 (m, 5H), 5.19 (s, 2H); MS (EI) *m/z* 271 (M^+, 14%), 227 (11%), 91 (100%).

To a solution of 4-(benzyloxycarbonylamino)benzoic acid (1.63 g, 6.00 mmol), EDC·HCl (1.38 g, 7.20 mmol) and DMAP (0.60 g, 0.60 mmol) in CH_2Cl_2 (10.0 mL) was added 5-hexene-1-ol (601 mg, 6.00 mmol). After the solution was refluxed for 2 h, the mixture was extracted with CH_2Cl_2 (100 mL) and water (100 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was applied to flash silica gel column chromatography (chloroform) to afford 5′-hexenyl 4-(benzyloxycarbonylamino)-benzoate (**14e**) as a colorless solid (1.27 g, 60%); mp 58–59 °C. ^{1}H NMR ($CDCl_3$): δ=7.99 (d, J=8.8 Hz, 2H), 7.47–7.35 (m, 7H), 6.93–6.87 (brs, NH), 5.87–5.77 (m, 1H), 5.22 (s, 2H), 5.03 and 4.98 (each d, J=17.1, 9.8 Hz, each 1H), 4.30 (t, J=7.1 Hz, 2H), 2.13 (q, J=7.1 Hz, 2H), 1.81–1.74 (m, 2H), 1.61–1.50 (m, 2H); ^{13}C NMR ($CDCl_3$): δ=166.2, 152.8, 142.0, 138.4, 135.7, 130.9, 128.7, 128.5, 128.4, 125.3, 117.6, 114.8, 67.3, 64.8, 33.3, 28.2, 25.3; MS (EI) *m/z* 353 (M^+, 5%), 271 (7%), 227 (9%), 163 (34%), 146 (100%), 108 (24%), 91 (72%), 82 (42%), 44 (46%). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.31; H, 6.53; N, 3.91.

4.1.7.13. *N*-Benzyloxycarbonyl-4-ethynylaniline (14f).[26] To a solution of 4-ethynylaniline (0.58 g, 5.00 mmol) in THF (10.0 mL) was added *N*-(benzyloxycarbonyloxy)succinimide (2.18 g, 9.00 mmol). The solution was stirred at room temperature for 36 h, after which time the solvent was removed under vacuum pressure. The residue was extracted with ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with water (30 mL), sat. $NaHCO_3$ solution (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was applied to flash silica gel column chromatography (hexane/ether=10:1) to afford *N*-benzyloxycarbonyl-4-ethynylaniline (**14f**) as a flesh-colored solid (1.17 g, 93%); mp 98.5–99 °C. ^{1}H NMR ($CDCl_3$): δ=7.45–7.34 (m, 9H), 6.70 (brs, NH), 5.20 (s, 2H), 3.02 (s, 1H); ^{13}C NMR ($CDCl_3$): δ=152.9, 138.3, 135.8, 133.0, 128.7, 128.5, 128.4, 118.2, 116.9, 83.5, 76.5, 67.2; MS (EI) *m/z* 251 (M^+, 22%), 207 (12%), 91 (100%). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.63; H, 5.24; N, 5.49.

4.1.7.14. Methyl 4-bromocinnamate (18). To a solution of 4-bromocinnamic acid (2.27 g, 10.0 mmol) in DMF (5.00 mL) was added *N*,*N*-dimethylformamide dimethylacetal (13.3 ml, 100 mmol). The solution was stirred at room temperature for 24 h, after which time the solvent was removed under vacuum pressure. The residue was extracted with ethyl acetate (100 mL) and water (100 mL). The organic layer was washed with sat. $NaHCO_3$ solution (100 mL), water (100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure to afford methyl 4-bromocinnamate (**18**) as a colorless solid (1.53 mg, 64%); mp 88–93 °C. ^{1}H NMR ($CDCl_3$): δ=7.62 (d, J=15.9 Hz, 1H), 7.52 (d, J=8.6 Hz, 2H), 7.38 (d, J=8.6 Hz, 2H), 6.43 (d, J=15.9 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$): δ=167.2, 143.5, 133.3, 132.1, 129.4, 124.5, 118.5, 51.8; MS (EI) *m/z* 242 (M^++H, 82%), 240 (M^+−H, 84%), 211 (97%), 209 (100%), 183 (24%), 181 (24%), 102 (86%). Anal. Calcd for $C_{10}H_9O_2Br$: C, 49.82; H, 3.76. Found: C, 49.83; H, 3.77.

4.1.7.15. Ethyl 4-(*N*-bezyloxyxcarbonylamino)cinnamate (19). To a solution of ethyl 4-aminocinnamate (761 mg, 4.00 mmol) in THF (10.0 mL) was added *N*-(benzyloxycarbonyloxy)succinimide (1.16 g, 4.80 mmol). The solution was refluxed for 48 h, after which time the solvent was removed under vacuum pressure. The residue was extracted with ethyl acetate (100 mL) and water (100 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was applied to flash silica gel column chromatography (hexane/ether=10:1) to afford ethyl 4-(*N*-bezyloxyxcarbonylamino)cinnamate (**19**) as a colorless solid (405 mg, 31%); mp 119–121 °C. ^{1}H NMR ($CDCl_3$): δ=7.62 (d, J=15.9 Hz, 1H), 7.35–7.49 (m, 9H), 6.78 (s, 1H), 6.34 (d, J=15.9 Hz, 1H), 5.21 (s, 2H), 4.25 (q, J=7.2 Hz, 2H), 1.33 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ=167.2, 153.0, 143.9, 139.6, 135.8, 129.7, 129.1, 128.7, 128.5, 128.4, 118.5, 116.9, 67.3, 60.4, 14.3; MS (EI) *m/z* 325 (M^+, 42%), 281 (20%), 91 (100%). Anal. Calcd for

$C_{19}H_{19}O_2NO_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.17; H, 5.94; N, 4.33.

4.1.8. General procedure of chemoselective hydrogenation using 2.5% Pd/Fib. After two vacuum/H_2 cycles to remove air from the round-bottom flask, a mixture of the substrate (1.00 mmol), 2.5% Pd/Fib (10 wt% of the substrate) in methanol (5.00 mL) was vigorously stirred at room temperature (ca. 20 °C) or at 50 °C under ambient pressure of hydrogen (balloon). The reaction mixture was filtered through a filter paper, and the filtrate was concentrated under reduced pressure to afford the product.

4.1.8.1. 3-Phenylpropiophenone (2a).[27] Yield 97% as a colorless solid; mp 74–75 °C. ^{1}H NMR ($CDCl_3$): δ=7.96 (d, J=7.3 Hz, 2H), 7.56 (t, J=7.3 Hz, 1H), 7.45 (t, J=7.3 Hz, 2H), 7.20–7.35 (m, 5H), 3.31 (t, J=7.6 Hz, 2H), 3.07 (t, J=7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ=199.2, 141.3, 136.9, 133.0, 128.6, 128.5, 128.4, 128.0, 126.1, 40.4, 30.1; MS (EI) m/z 210 (M^+, 65%), 105 (100%), 77 (40%). Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.71. Found: C, 85.54; H, 6.68.

4.1.8.2. 1,5-Diphenylpentane-1-one (2b).[28] Yield 100% as a yellow oil. ^{1}H NMR ($CDCl_3$): δ=7.94 (d, J=7.3 Hz, 2H), 7.14–7.57 (m, 8H), 2.99 (t, J=7.3 Hz, 2H), 2.67 (t, J=7.6 Hz 2H), 1.68–1.84 (m, 4H); ^{13}C NMR ($CDCl_3$): δ=142.2, 137.0, 132.9, 128.5, 128.4, 128.3, 128.0, 125.8, 125.7, 38.4, 35.8, 31.1, 24.0; MS (EI) m/z 238 (M^+, 29%), 133 (34%), 120 (87%), 105 (100%), 91 (40%), 77 (60%); HRMS (EI) Calcd for $C_{17}H_{18}O$ (M^+): 238.1358. Found: 238.1365.

4.1.8.3. 4-Hydroxy-3-propylacetophenone (2c). Yield 99% as a green solid; mp 93–95 °C. ^{1}H NMR ($CDCl_3$): δ=7.79 (s, 1H), 6.91 and 7.73 (each d, J=8.3 Hz, each 1H), 2.64 (t, J=7.8 Hz, 2H), 2.58 (s, 3H), 1.64–1.69 (m, 2H), 0.97 (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ=198.7, 159.4, 131.2, 129.5, 129.1, 128.6, 115.1, 31.9, 26.2, 22.6, 13.9; MS (EI) m/z 178 (M^+, 30%), 163 (100%), 149 (23%). Anal. Calcd for $C_{11}H_{14}O_2 \cdot 1/10$: C, 73.39; H, 7.95. Found: C, 73.46; H, 7.95.

4.1.8.4. 2-Propyl-4,6-dibenzoylresorcinol (2d). Yield 74% as a light green solid; mp 167–169 °C. ^{1}H NMR ($CDCl_3$): δ=13.16 (s, 2H), 7.88 (s, 1H), 7.38–7.58 (m, 12H), 2.76 (t, J=7.6 Hz, 2H), 1.62–1.71 (m, 2H), 1.04 (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ=200.3, 167.4, 140.4, 137.5, 131.9, 128.8, 118.4, 112.0, 24.1, 21.6, 14.2; MS (EI) m/z 360 (M^+, 55%), 332 (24%), 331 (100%), 332 (24%), 253 (16%), 175 (33%), 105 (16%), 77 (16%). Anal. Calcd for $C_{23}H_{20}O_4$: C, 76.65; H, 5.59. Found: C, 76.44; H, 5.64.

4.1.8.5. 3-Benzoylpropionic acid (2e). Commercially available (Aldrich), 98% as a yellow solid; mp 117–119 °C. ^{1}H NMR ($CDCl_3$): δ=7.98 (d, J=7.4 Hz, 2H), 7.57 (t, J=7.4 Hz, 1H), 7.47 (t, J=7.4 Hz, 2H), 3.32 (t, J=6.6 Hz, 2H), 2.82 (t, J=6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ=197.8, 178.5, 136.4, 133.3, 128.0, 33.1, 28.0; MS (EI) m/z 178 (M^+, 8%), 105 (100%), 77 (39%). Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.39; H, 5.66. Found: C, 67.55; H, 5.59.

4.1.8.6. 3-(4-Methylbenzoyl)propionic acid (2f). Commercially available (Aldrich), 99% as a light green solid; mp 129–131 °C. ^{1}H NMR ($CDCl_3$): δ=7.26 and 7.88 (each d, J=8.3 Hz, each 2H), 3.29 (t, J=6.6 Hz, 2H), 2.81 (t, J=6.6 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$): δ=197.5, 178.8, 144.1, 133.9, 129.3, 128.2, 33.0, 28.1, 21.6; MS (EI) m/z 192 (M^+, 10%), 119 (100%), 91 (32%), 65 (10%). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.72; H, 6.30. Found: C, 68.73; H, 6.27.

4.1.8.7. 4-(2-Phenylethyl)benzaldehyde (2g).[29] Yield 100% as a light yellow solid. ^{1}H NMR ($CDCl_3$): δ=9.97 (s, 1H), 7.79 (d, J=8.3 Hz, 2H), 7.14–7.32 (m, 9H), 2.92–3.03 (m, 4H); ^{13}C NMR ($CDCl_3$): δ=192.0, 149.1, 140.9, 134.6, 129.9, 129.2, 128.4, 126.2, 38.0, 34.7; MS (EI) m/z 210 (M^+, 35%), 107 (28%), 91 (100%), 77 (25%). Anal. Calcd for $C_{15}H_{14}O \cdot 1/2H_2O$: C, 82.16; H, 6.89. Found: C, 82.51; H, 6.56.

4.1.8.8. 2-Propyloxybenzaldehyde (2h).[30] Yield 100% as a light yellow oil. ^{1}H NMR ($CDCl_3$): δ=10.53 (s, 1H), 7.83 (dd, J=1.4, 7.9 Hz, 1H), 7.53 (dt, J=0.65, 7.9 Hz, 1H), 7.01 (t, J=7.9 Hz, 1H), 6.98 (d, J=7.9 Hz, 1H), 4.05 (t, J=6.8 Hz, 2H), 1.84–1.93 (m, 2H), 1.08 (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ=189.9, 189.8, 161.6, 135.9, 128.2, 120.5, 112.5, 70.0, 22.5, 10.5; MS (EI) 166 (M^++2, 25%), m/z 164 (M^+, 28%), 123 (65%), 121 (100%), 120 (35%), 57 (29%); HRMS (EI) Calcd for $C_{10}H_{12}O_2$ (M^+): 164.0837. Found: 164.0835.

4.1.8.9. Methylmanderate (2i). Commercially available (Aldrich), 98% as a colorless solid. ^{1}H NMR ($CDCl_3$): δ=7.30–7.43 (m, 5H), 5.18 (s, 1H), 3.76 (s, 3H).

4.1.8.10. Benzoin (2j). Commercially available (Aldrich), 98% as a colorless solid. ^{1}H NMR ($CDCl_3$): δ=7.92 (d, J=7.7 Hz, 2H), 7.53 (t, J=7.7 Hz, 1H), 7.40 (t, J=7.7 Hz, 2H), 7.34–7.27 (m, 5H), 5.96 (d, J=6.1 Hz, 1H), 4.55 (d, J=6.1 Hz, OH).

4.1.8.11. 4-Chloroethylbenzene (6e). Commercially available (TCI), 100%. ^{1}H NMR ($CDCl_3$): δ=7.14 and 7.22 (each d, J=8.3 Hz, each 2H), 2.59 (q, J=7.7 Hz, 2H), 1.86 (t, J=7.7 Hz, 3H); MS (EI) m/z 140 (M^+, 35%), 127 (31%), 125 (100%), 105 (40%).

4.1.8.12. 4′-Chloro-3-phenylpropiophenone (6f).[31] Yield 98% as a colorless solid; mp 78–80 °C. ^{1}H NMR ($CDCl_3$): δ=7.42, 7.89 (each d, J=8.3 Hz, each 2H), 7.19–7.32 (m, 5H), 2.37 (t, J=7.7 Hz, 2H), 3.06 (t, J=7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ=198.0, 141.0, 139.5, 135.2, 129.5, 128.9, 128.5, 128.4, 126.2, 40.4, 30.0; MS (EI) m/z 246 (M^+, 15%), 244 (55%), 141 (34%), 139 (100%), 111 (30%), 105 (15%), 91 (14%), 77 (13%); HRMS (EI) Calcd for $C_{15}H_{13}OCl$ (M^+): 244.0655. Found: 244.0661. Anal. Calcd for $C_{15}H_{13}OCl$: C, 73.62; H, 5.35. Found: C, 73.70; H, 5.21.

4.1.8.13. 3-(4-Chlorophenyl)propiophenone (6g).[32] Yield 99% as a light green solid; mp 53–55 °C. ^{1}H NMR ($CDCl_3$): δ=7.94 (d, J=6.8 Hz, 2H), 7.17–7.60 (m, 7H), 3.04 and 3.28 (each t, J=7.6 Hz, each 2H); ^{13}C NMR ($CDCl_3$): δ=198.8, 139.7, 133.1, 129.8, 129.5, 129.2, 128.5, 128.0, 122.5, 40.1, 29.3; MS (EI) m/z 244 (M^+,

48%), 105 (100%), 77 (42%). Anal. Calcd for $C_{15}H_{13}OCl$: C, 73.62; H, 5.35. Found: C, 73.66; H, 5.34.

4.1.8.14. 2,3-Dichloro-4-*sec*-pentanoylphenoxyacetic acid (6h).[33] Yield 100% as a colorless solid. ^{1}H NMR ($CDCl_3$): δ=6.80 and 7.27 (each d, J=8.6 Hz, each 2H), 4.81 (s, 2H), 3.17–3.82 (m, 1H), 1.75–7.82 (m, 1H), 1.41–1.47 (m, 1H), 1.17 (d, J=6.8 Hz, 3H), 0.93 (t, J=7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ=206.6, 172.5, 155.5, 135.2, 131.4, 126.9, 110.8, 65.6, 46.8, 26.0, 15.6, 11.6; MS (FAB: Gly) m/z 307 (M^++2, 15%), 305 (M^+, 25%). Anal. Calcd for $C_{13}H_{14}O_4Cl\cdot 1/4H_2O$: C, 50.56; H, 4.74. Found: C, 50.64; H, 4.65.

4.1.8.15. 2-Chlorobenzylamine (6i). Commercially available (TCI), 91% as a colorless oil. ^{1}H NMR ($CDCl_3$): δ=7.18–7.39 (m, 4H), 3.94 (s, 2H), 2.57 (s, 1H); MS (EI) 265 (20%), 264 (18%), 230 (17%), 154 (19%) m/z 140 (M^+−1, 25%), 127 (29%), 125 (100%), 91 (25%), 89 (24%).

4.1.8.16. 4-Bromoethylbenzene (6j). Commercially available (TCI), 100%. ^{1}H NMR ($CDCl_3$): δ=7.17 and 7.44 (each d, J=8.3 Hz, each 2H), 2.66 (q, J=7.7 Hz, 2H), 1.26 (t, J=7.7 Hz, 3H).

4.1.8.17. Dipropyl 2,3,4,5-tetrabromophthalate (6k).[34] Yield 94% as a colorless solid; mp 61–62 °C. ^{1}H NMR ($CDCl_3$): δ=4.27 (t, J=6.6 Hz, 4H), 1.75 (m, 4H), 1.01 (t, J=7.6 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ=164.8, 138.3, 135.4, 132.0, 122.7, 68.5, 21.7, 10.4; MS (EI) m/z 566 (M^+, 12%), 524 (9%), 483 (29%), 482 (40%), 481 (30%), 466 (60%), 465 (100%), 464 (65%), 420 (12%).

4.1.8.18. Benzyl propionate (10b). Commercially available (Aldrich), 91% determined by ^{1}H NMR. ^{1}H NMR (THF-d_8): δ=7.29–7.20 (m, 5H), 5.02 (m, 2H), 2.29–2.25 (m, 2H), 1.02 (t, J=7.8 Hz, 3H).

4.1.8.19. Benzyl isobutylate (10c). Commercially available (TCI), 93% determined by ^{1}H NMR. ^{1}H NMR (THF-d_8): δ=7.29–7.20 (m, 5H), 5.02 (s, 2H), 2.52–2.46 (m, 1H), 1.08 (d, J=7.0 Hz, 6H).

4.1.8.20. Benzyl 2-methylbutylate (10d).[35] 77% as a colorless oil. ^{1}H NMR ($CDCl_3$): δ=7.36–7.31 (m, 5H), 5.12 (s, 2H), 2.45–2.40 (m, 1H), 1.74–1.67 (m, 1H), 1.53–1.46 (m, 1H), 1.16 (d, J=7.2 Hz, 3H), 0.90 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ=176.6, 136.3, 128.5, 128.1, 128.0, 66.0, 41.1, 26.8, 16.6, 11.6; MS (EI) m/z 192 (M^+, 25%), 181 (67%), 180 (50%), 179 (40%), 165 (25%), 108, (20%), 91 (100%), 57 (43); HRMS (EI) Calcd for $C_{12}H_{16}O_2$ (M^+): 192.1150. Found: 192.1156.

4.1.8.21. Benzyl propyloxyacetate (10e). Yield 99% as a light brown oil. ^{1}H NMR ($CDCl_3$): δ=7.37–7.33 (m, 5H), 5.20 (s, 2H), 4.12 (s, 2H), 3.49 (t, J=7.2 Hz, 2H), 1.69–1.60 (m, 2H), 0.93 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ=170.5, 135.5, 128.5, 128.4, 73.5, 68.2, 66.4, 22.7, 10.4; MS (FAB, NBA) m/z 209 (M^++H, 20%); HRMS (FAB, NBA) Calcd for $C_{12}H_{17}O_3$ (M^++H): 209.1178. Found: 209.1172.

4.1.8.22. Benzyl 3-phenylpropionate (10f).[36] Yield 98% as a colorless oil. ^{1}H NMR ($CDCl_3$): δ=7.18–7.37 (m, 10H), 5.11 (s, 2H), 2.97 (t, J=7.8 Hz, 2H), 2.69 (t, J=7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ=173.0, 140.7, 136.2, 128.8, 128.6, 128.5, 126.6, 66.6, 36.1, 31.2; MS (EI) m/z 240 (M^+, 5%), 180 (60%), 149 (26%), 107 (78%), 91 (100%), 77 (15%); HRMS (EI) Calcd for $C_{16}H_{16}O_2$ (M^+): 240.1150. Found: 2240.1160.

4.1.8.23. Benzyl 4-ethylbenzoate (10g). Yield 97% as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ=8.00 (d, J=8.3 Hz, 2H), 7.46–7.25 (m, 7H), 5.36 (s, 2H), 2.70 (q, J=7.7 Hz, 2H), 1.25 (t, J=7.7 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ=166.5, 149.9, 136.2, 129.8, 128.5, 128.1, 127.9, 127.6, 126.1, 66.4, 28.9, 15.2; MS (EI) m/z 240 (M^+, 30%), 133 (100%), 91 (36%); HRMS (EI) Calcd for $C_{16}H_{16}O_2$ (M^+): 240.1150. Found: 224. 1139.

4.1.8.24. Benzyl-2-(benzyloxycarbonyl)propionate (10h). Yield 100% as a colorless oil. ^{1}H NMR ($CDCl_3$): δ=7.95 (d, J=7.2 Hz, 1H), 7.44–7.24 (m, 13H), 5.33 (s, 2H), 5.09 (s, 2H), 3.30 (t, J=7.7 Hz, 2H), 2.70 (t, J=7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ=172.8, 167.0, 142.5, 136.0, 135.9, 132.3, 131.2, 131.0, 129.3, 128.6, 128.5, 128.3, 128.3, 128.2, 128.2, 128.1, 126.5, 66.7, 66.2, 35.8, 29.9; MS (EI) m/z 374 (M^+, 3%), 265 (10%), 177 (53%), 149 (18%), 91 (100%); HRMS (EI) Calcd for $C_{24}H_{22}O_4$ (M^+): 374.1511. Found: 374.1518.

4.1.8.25. Benzyl 4-aminomethylbenzoate (10i).[37] Yield 100%. ^{1}H NMR ($CDCl_3$): δ=8.04 (d, J=8.3 Hz, 2H), 7.46–7.26 (m, 7H), 5.36 (s, 2H), 3.94 (s, 2H); MS (EI) m/z 241 (M^+, 20%), 240 (29%), 150 (40%), 134 (75%), 106 (100%), 91 (90%).

4.1.8.26. *N*-Benzyloxycarbonyl-4-ethylaniline (16b).[2a] Yield 97% as a pale yellow powder; mp 72–72.5 °C. ^{1}H NMR ($CDCl_3$): δ=7.41–7.26 (m, 7H), 7.13 (d, J=8.3 Hz, 2H), 6.60 (brs, NH), 5.19 (s, 2H), 2.60 (q, J=7.6 Hz, 2H), 1.21 (t, J=7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ=153.5, 139.6, 136.2, 135.4, 128.6, 128.3, 128.3, 119.0, 66.9, 28.2, 15.7.

4.1.8.27. *N*-Benzyloxycarbonyl-*N*-propylaniline (16c). Yield 97% as a light brown oil. ^{1}H NMR ($CDCl_3$): δ=7.37–7.19 (m, 10H), 5.14 (s, 2H), 3.64 (t, J=7.4 Hz, 2H), 1.59–1.43 (m, 2H), 0.87 (t, J=7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ=155.5, 141.9, 136.8, 128.9, 128.3, 127.7, 127.5, 127.3, 126.6, 67.0, 52.1, 21.5, 11.1; MS (EI) m/z 269 (M^+, 30%), 196 (20%), 91 (100%); HRMS (EI) Calcd for $C_{17}H_{19}NO_2$ (M^+): 269.1420. Found: 269.1416.

4.1.8.28. 3-Phenylpropyl *N*-(benzyloxycarbonyl)-anthranilate (16d). Yield 99% as a pale yellow solid; mp 40–41 °C. ^{1}H NMR ($CDCl_3$): δ=10.59 (s, NH), 8.46 (d, J=7.8 Hz, 1H), 7.97 (d, J=7.8 Hz, 1H), 7.53 (t, J=7.8 Hz, 1H), 7.43–7.20 (m, 5H), 5.21 (s, 2H), 4.32 (t, J=7.0 Hz, 2H), 2.78 (t, J=7.0 Hz, 2H), 2.14–2.07 (m, 2H); ^{13}C NMR ($CDCl_3$): δ=168.0, 153.4, 141.7, 140.9, 136.1, 134.5, 130.8, 128.5, 128.4, 128.2, 126.1, 118.8, 114.7, 66.8, 64.6, 32.3, 30.1; MS (EI) m/z 389 (M^+, 10%), 226 (9%), 208 (18%), 118 (40%), 117 (32%), 91 (100%); HRMS (EI) Calcd for $C_{24}H_{23}NO_4$ (M^+): 389.1633. Found: 389.1627.

4.1.8.29. Hexyl 4-(benzyloxycarbonylamino)benzoate (16e). Yield 100% as a colorless solid; mp 85–86 °C. ^{1}H NMR ($CDCl_3$): δ=7.99 (d, J=8.8 Hz, 2H), 7.47–7.34 (m, 7H), 6.86 (brs, NH), 5.22 (s, 2H), 4.29 (t, J=7.0 Hz, 2H), 1.78–1.71 (m, 2H), 1.43–1.32 (m, 6H), 0.90 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ=166.2, 152.8, 141.9, 135.7, 130.9, 128.7, 128.5, 128.4, 125.4, 117.6, 67.4, 65.0, 31.5, 28.7, 25.7, 22.5, 14.0; MS (EI) *m/z* 355 (M^+, 18%), 311 (12%), 163 (44%), 146 (42%), 91 (100%); HRMS (EI) Calcd for $C_{21}H_{25}NO_4$ (M^+): 355.1784. Found: 355.1793.

4.1.8.30. Dihydrojasmone (21). Commercially available (TCI), 60% as a colorless oil. ^{1}H NMR ($CDCl_3$): δ=2.49–2.47 (m, 2H), 2.37–2.47 (m, 2H), 2.16 (t, J=7.3 Hz, 2H), 2.05 (s, 3H), 1.68–1.24 (m, 6H), 0.87 (t, J=7.3 Hz, 3H); MS (EI) *m/z* 166 (M^+, 15%), 151 (58%), 137 (30%), 123 (25%), 110 (100%), 105 (24%), 81 (24%), 67 (29%); HRMS (EI) Calcd for $C_{11}H_{18}O$ (M^+): 166.1358. Found: 166.1364.

4.1.9. General procedure of hydrogenation using 5% Pd/C or Pd/C(en) (Schemes 7 and 8). After two vacuum/H_2 cycles to remove air from the reaction tube, a mixture of the substrate (1.00 mmol), 5% Pd/C or Pd/C(en) (10 wt% of the substrate) in the solvent (1.00 mL) was vigorously stirred at room temperature (ca. 20 °C) or at 50 °C under ambient pressure of hydrogen (balloon). The reaction mixture was filtered using a membrane filter (Millipore Millex®-LG, 0.20 μm). The quantitative conversion of **11** and **14a**, and the product ratio of **7f** and **14b** were confirmed by ^{1}H NMR of the crude mixture.

Acknowledgements

We are very grateful to Drs Hiromi Yamada and Kozo Tsubouchi of National Institute of Agrobiological Sciences for valuable discussions and help with the preparation of Pd/Fib catalyst.

References and notes

1. For selected reviews on reductions, see: (a) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999. (b) Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; Wiley-Interscience: New York, 2001. (c) Hudlicky, M. *Reductions in Organic Chemistry*, 2nd ed.; ACS: Washington, DC, 1996. (d) Rylander, P. N. *Hydrogenation Methods*; Academic: New York, 1985.
2. For example, see: (a) Sajiki, H.; Hattori, K.; Hirota, K. *J. Org. Chem.* **1998**, *63*, 7990–7992. (b) Sajiki, H.; Hattori, K.; Hirota, K. *Chem. Eur. J.* **2000**, *6*, 2200–2204. (c) Sajiki, H.; Hirota, K. *J. Synth. Org. Chem. Jpn* **2001**, *59*, 109–120 and references cited therein.
3. Commercially available from Wako Pure Chemical Industires, Ltd. (Japan) as palladium-activated carbon ethylene diamine complex (Pd 5%) [5% Pd/C(en), 163-21441 and 169-21443].
4. Robson, R. M. In *Handbook of Fiber Chemistry*; Lewin, M., Pearce, E. M., Eds. 2nd ed.; Marcel Dekker: New York, 1998.
5. (a) Lucas, F. *Nature* **1966**, *210*, 952–953. (b) Mita, K.; Ichimura, S.; James, T. C. *J. Mol. Evol.* **1994**, *38*, 583–592.
6. (a) Hojo, N.; Shirai, H. *SEN-I GAKKAISHI* **1966**, *22*, 527–531. (b) Koide, N.; Inagaki, N.; Katsuura, K. *SEN-I GAKKAISHI* **1977**, *33*, T166–T169. (c) Shimizu, F.; Sakaguchi, I. *SEN-I GAKKAISHI* **1980**, *36*, T127–T131.
7. (a) Akabori, S.; Sakurai, S.; Izumi, Y.; Fujii, Y. *Nature* **1956**, *178*, 323–324. (b) Izumi, Y. *Bull. Chem. Soc. Jpn* **1959**, *32*, 932–936. 936–942 and 942–945. (c) Akamatsu, A.; Izumi, Y.; Akabori, S. *Bull. Chem. Soc. Jpn* **1961**, *34*, 1067–1072. (d) Akamatsu, A.; Izumi, Y.; Akabori, S. *Bull. Chem. Soc. Jpn* **1961**, *35*, 1706–1711.
8. Zhou, Y.; Chen, W.; Itoh, H.; Naka, K.; Ni, Q.; Yamane, H.; Chujo, Y. *Chem. Commun.* **2001**, 2518–2519.
9. Sajiki, H.; Ikawa, T.; Hirota, K. *Tetrahedron Lett.* **2003**, *44*, 171–174. Sajiki, H.; Ikawa, T.; Hirota, K. *Tetrahedron Lett.* **2003**, *57*, 4837–4839.
10. Day, R. A.; Underwood, A. L. *Quantitative Analysis*; Prentice-Hall: Engewood Cliffs, 1967.
11. Nash, T. *Biochemistry* **1953**, *55*, 416–421.
12. Sajiki, H.; Hattori, K.; Hirota, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4043–4044. Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2001**, *57*, 4817–4824.
13. It is well known that aromatic chlorides are much less reactive than aromatic bromides and iodides and, hence, the dechlorination of aromatic chloride cannot readily be achieved and the hydrodechlorination reactions are very frequently incomplete,[1] see: (a) Hara, R.; Sato, K.; Sun, W.-H.; Takahashi, T. *Chem. Commun.* **1999**, 845–846. (b) Sajiki, H.; Kume, A.; Hattori, K.; Hirota, K. *Tetrahedron Lett.* **2002**, *43*, 7247–7250.
14. Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.
15. Misiti, D.; Zappia, G.; Monach, G. D. *Synthesis* **1999**, 873–877.
16. (a) Kuzuhara et al. have reported the chemoselective hydrogenation of an azido group in the presence of an aliphatic *N*-Cbz protective group using Raney Ni, which must be added into the reaction mixture in small portions with careful monitoring to avoid cleavage of the *N*-Cbz group. Kuzuhara, H.; Mori, O.; Emoto, S. *Tetrahedron Lett.* **1976**, 379–382. (b) Shinada and Ohfune et al. reported a chemoselective hydrogenation of olefin and benzyl ester functionalities in the presence of *N*-Cbz and benzyl ether protective groups using Pd/C while the stability of the *N*-Cbz group under the conditions was time-dependent. Shinada, T.; Hayashi, K.; Yoshida, Y.; Ohfune, Y. *Synlett* **2000**, 1506–1508.
17. Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2000**, *56*, 8433–8441.
18. We have quite recently reported the frequent and unexpected cleavage of *tert*-butyldimethylsilyl (TBDMS) ethers to form the parent alcohols under mild hydrogenation conditions using 10% Pd/C in MeOH although TBDMS ethers have been believed to be stable under hydrogenation conditions. Furthermore, we have reported a remarkable solvent effect toward the Pd/C-catalyzed cleavage of TBDMS and triethylsilyl (TES) ethers and it was applied to the development of a chemoselective hydrogenation method for olefin, benzyl ether and acetylene functionalities distinguishing from the TBDMS and TES protective groups of a hydroxy group by the employment of EtOAc or MeCN as a solvent. See: Sajiki, H.; Ikawa, T.; Hattori, K.; Hirota, K. *Chem. Commun.* **2003**, 654–655. Ikawa, T.; Sajiki, H.; Hattori, K.; Hirota, K. *Tetrahedron* **2004**, *60*, 6901–6911 and references cited therein.

19. Bergman, M.; Zervas, L. *Ber.* **1932**, *65*, 1192–1201.
20. Quite a few methods to maintain the benzyl ester intact during a synthetic process involving conjugate reduction (non-hydrogenation) steps have been reported. (a) Mathoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291–293. (b) Evans, D. A.; Fu, G. C. *J. Org. Chem.* **1990**, *55*, 5678–5680. (c) Kelly, T. R.; Xu, W.; Ma, Z.; Li, Q.; Bhushan, V. *J. Am. Chem. Soc.* **1993**, *115*, 5843–5844.
21. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
22. Goldwasser, J. M.; Leznoff, C. C. *Can. J. Chem.* **1978**, *56*, 1562–1568.
23. Ali, A.; Robinson, J. B. *J. Pharm. Pharmacol.* **1991**, *43*, 750–757.
24. Salvatore, R. N.; Shin, S.; Nagle, A. S.; Jung, K. W. *J. Org. Chem.* **2001**, *66*, 1035–1037.
25. Krzyzanowski, L.; Rzeszotarska, B. *Org. Preparations Procedures Int.* **1985**, *17*, 83–89.
26. Ishizaki, M.; Zyo, M.; Kasama, Y.; Niimi, Y.; Hoshino, O.; Nishitani, K.; Hara, H. *Heterocycles* **2003**, *60*, 2259–2271.
27. Fleming, I.; Newton, T. W.; Sabin, V.; Zammattio, F. *Tetrahedron* **1992**, *48*, 7793–7802.
28. Zheng, B.; Srebnik, M. *J. Org. Chem.* **1995**, *60*, 3278–3279.
29. Matsuhashi, H.; Kuroboshi, M.; Hatanaka, Y.; Hiyama, T. *Tetraherdon Lett.* **1994**, *35*, 6507–6510.
30. Wang, J.; Fan, X.; Feng, X.; Qian, Y. *Synthesis* **1989**, 291–292.
31. Saito, S.; Sato, Y.; Ohwada, T.; Shudo, K. *J. Am. Chem. Soc.* **1994**, *116*, 2312–2317.
32. Huang, X.; Zhang, H. *Synth. Commun.* **1989**, *19*, 97–105.
33. Abraham, D. J.; Mehanna, A. S.; Williams, F. S.; Cragoe, E. J. Jr.; Woltersdorf, O. W., Jr. *J. Med. Chem.* **1989**, *32*, 2460–2467.
34. Langer, S. H.; Zahn, C.; Vial, M. H. *J. Org. Chem.* **1959**, *24*, 423–425.
35. Shilina, I.; Nagasue, H. *Tetrahedron Lett.* **2002**, *43*, 5837–5840.
36. Page, P.; Bulman, M.; Michael, J.; Allin, S.; Buckle, D. R. *Tetrahedron* **2000**, *56*, 9683–9695.
37. Amat, L.; Carbo-Dorca, R.; Ponec, R. *J. Med. Chem.* **1999**, *42*, 5169–5180.