A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201711363
Angew. Chem. 10.1002/ange.201711363

Link to VoR: http://dx.doi.org/10.1002/anie.201711363
http://dx.doi.org/10.1002/ange.201711363

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10.1002/anie.201711363

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Chemoselectivity Control in the Asymmetric Hydrogenation of γ- and δ-Keto Esters into the Hydroxy Esters or the Diols

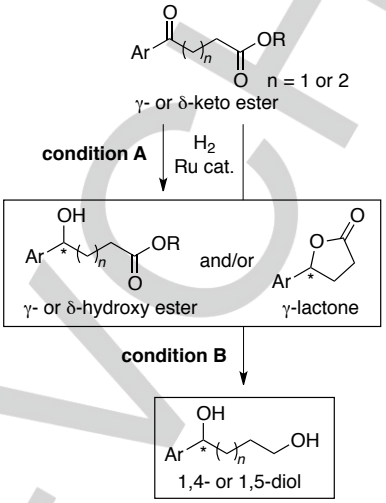
Noriyoshi Arai, Takanori Namba, Kei Kawaguchi, Yuki Matsumoto, and Takeshi Ohkuma*

Abstract: Asymmetric hydrogenation of aromatic γ- and δ-keto esters into the optically active hydroxy esters or the diols catalyzed by a novel DIPSkewphos/3-AMIQ–Ru(II) complex was studied. Under the optimized conditions (8 atm H_2, Ru complex/*t*-C_4H_9OK = 1:3.5, 25°C) the γ- and δ-hydroxy esters (including γ-lactones) were obtained in 97%–99% *ee* quantitatively. When the reaction was conducted under slightly harsh conditions (20 atm H_2, [*t*-C_4H_9OK] = 50 mM, 40°C), the 1,4- and 1,5-diols were predominantly obtained in 95%–99% *ee*. The reactivity of the ester group was notably dependent on the length of the carbon-spacer between the two carbonyl moieties of the substrate. The reaction of β- and ε-keto esters selectively afforded the hydroxy esters regardless of the reaction conditions. This catalyst system was applied to the enantioselective and ester regio (position)-selective hydrogenation of a γ-ε-diketo diester into the tri-hydroxy ester.

Enantioselective hydrogenation of keto esters without reduction of the ester groups is an efficient method to produce the corresponding chiral hydroxy esters and lactones.[1] Several well-designed chiral catalysts have been developed and utilized even in industrial-scale reactions. The BINAP–Ru-catalyzed hydrogenation of β-keto esters developed by Noyori and co-workers is a representative example.[1,2] Asymmetric hydrogenation of keto esters into the chiral diols is also an important transformation. The catalyst should exhibit high enantioselectivity for the reaction of the keto-carbonyl groups, and also should show high activity for the reduction of the less reactive ester moieties. Recently, Zhou and co-workers reported that the Ir complex with a chiral P–N–N tridentate ligand catalyzed asymmetric hydrogenation of δ-aryl-δ-keto esters into the chiral 1,5-diols in excellent enantiomeric excess (*ee*).[3] The reactivity of the ester group was dependent on the substrate structure, so that the hydrogenation of the γ-keto ester gave a mixture of the 1,4-diol, the γ-hydroxy ester, and the γ-lactone.

We then aimed to develop a novel chiral catalyst that selectively transforms keto esters into either the hydroxy esters or the diols in high enantiomeric purity just by changing the reaction conditions (Scheme 1).[4] Enantiomerically enriched hydroxy esters and diols are both useful synthetic intermediates.

We recently devised [RuX_2(diphosphane)(pica)] (X = Cl, Br; diphosphane = BINAPs, XylSkewphos; PICA = α-picolylamine; see the structure **5a** for example),[5] which efficiently catalyzes asymmetric hydrogenation of sterically congested *tert*-alkyl ketones, 3-quinuclidinone with a bicyclo[2.2.2] cyclooctane



• Chemoselectivity is controlled by changing the reaction conditions.

Scheme 1. Chemo- and enantioselective hydrogenation of γ- and δ-keto esters.

skeleton, and acyl silanes in the presence of base.[6,7] The flat shape of the PICA ligand seems to provide a large pocket close to the reaction site for substrates.

We next focused our attention on the electronic properties of the PICA ligands, which have both alkyl amine and pyridine coordinative sites, on the hydrogenation catalysis. Keto esters with two different carbonyl groups were suitable substrates to examine the catalyst efficiency. We here describe asymmetric hydrogenation of aromatic γ- and δ-keto esters catalyzed by the novel [$RuBr_2$(dipskewphos)(3-amiq)][5] and *t*-C_4H_9OK system (Scheme 1). The corresponding γ- and δ-hydroxy esters (including γ-lactones) were obtained in excellent enantiomeric purity under the optimized conditions (condition A). When the reaction was conducted under slightly harsh conditions (condition B), the 1,4- and 1,5-diols in high *ee* were predominantly obtained.

Hydrogenation of *tert*-butyl 4-oxo-4-phenylbutanoate (**1a**; 0.53 mmol), an aromatic γ-keto ester, in ethanol (1.1 mL) with [$RuBr_2${(*S*,*S*)-xylskewphos}(pica)] ((*S*,*S*)-**5a**; 1.1 μmol, substrate/catalyst molar ratio (S/C) = 500:1) and *t*-C_4H_9OK (5.0 mM in ethanol, 5.8 μmol, catalyst/base molar ratio = 1:5) at 25°C under 8 atm of H_2 in 2 h afforded a mixture of *tert*-butyl 4-hydroxy-4-phenylbutanoate (**2a**, 41%, 80% *ee*), ethyl 4-hydroxy-4-phenylbutanoate (**2b**, 28%, 77% *ee*), 4-phenyl-γ-butyrolactone (**3a**, 21%, 77% *ee*), and 1-phenyl-1,4-butanediol (**4a**, 10%, 95% *ee*) (Table 1, entry 1).[8] The finding that the enantiomeric purity of **4a** was higher than those of **2a**, **2b**, and **3a** suggested that partial kinetic resolution occurred through the hydrogenation of ester moieties. Excellent enantiomeric purity of 98% for the mono-hydrogenated products, **2a** and **2b**, was obtained when the sterically more demanding diphosphane ligand DIPSkewphos was coupled with an isoquinoline-PICA analogue

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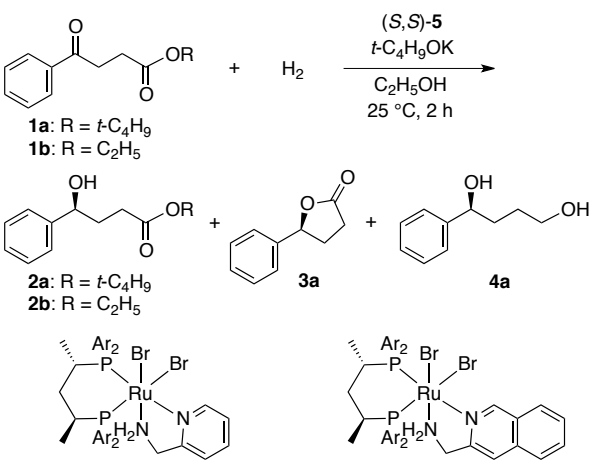
10.1002/anie.201711363

Table 1. Asymmetric hydrogenation of γ-keto esters **1**.[a]



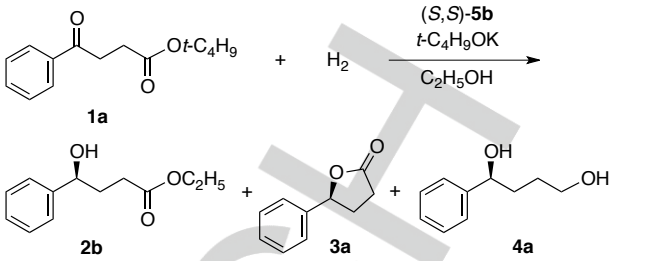
Entry	**5**	**5**/base[b]	[base][c]	Yield [%][d], *ee* [%][e]			
				2a	**2b**	**3a**	**4a**
1	**5a**	1:5	5.0	41, 80	28, 77	21, 77	10, 95
2	**5b**	1:5	5.0	79, 98	6, 98	11, 98	4, 99
3[f]	**5b**	1:5	5.0	–	40, 98	54, 98	6, 99
4	**5b**	1:5	2.5	89, 98	2, 97	8, 98	1, 99
5	**5b**	1:5	1.0	85, 99	2, 98	11, 98	<1, nd
6	**5b**	1:3.5	1.0	92,[g] 99	<1, nd	2, 99	<1, nd
7[h]	**5b**	1:2.5	1.0	90, 96	<1, nd	<1, nd	<1, nd

[a] Unless otherwise stated, reactions were conducted at 25°C under 8 atm of H_2 for 2 h using 0.51–0.67 mmol of γ-keto ester **1a** in ethanol containing Ru complexes (*S*,*S*)-**5** and *t*-C_4H_9OK. **1a**/**5** = 500:1. Complete conversion of **1a** was observed. [b] **5**/*t*-C_4H_9OK molar ratio. [c] Concentration of *t*-C_4H_9OK [mM] in the reaction mixture. [d] Determined by ^1H NMR analysis. [e] Determined by HPLC analysis on a chiral stationary phase. The *ee* value of **4a** was determined after conversion to the diacetate. nd: not determined. [f] The ethyl ester **1b** was used as a substrate. [g] 92% isolated yield. [h] 90% conversion in 24 h.

3-AMIQ on the Ru complex (**5b**) (entry 2). The yield of the diol **4a** was reduced to 4%. The same enantioselectivity was obtained in the reaction of the ethyl ester **1b**, although an approximately 1:1.4 mixture of **2b** and **3a** was obtained (entry 3). Hydrogenation of the ester moiety was suppressed by decreasing the amount and concentration of base (entries 4–7). Thus, the hydroxy ester **2a** and a small amount of the lactone **3a**, both in 99% *ee*, were obtained by using 3.5 equivalents of *t*-C_4H_9OK (1.0 mM) to the complex **5b** (entry 6). No detectable amount of the diol **4a** was obtained under the conditions used. The reaction was not completed even after 24 h under the less basic conditions (*t*-C_4H_9OK/**5b** = 2.5:1, [*t*-C_4H_9OK] = 1.0 mM) (entry 7). Notably, no hydrogenation was observed when the [$RuCl_2${(*S*)-binap}{(*S*,*S*)-dpen}] and *t*-C_4H_9OK system was used as a catalyst. This system is known as a highly active catalyst in the hydrogenation of unfunctionalized ketones.[9]

The product composition was dramatically changed by tuning the reaction conditions as shown in Table 2. Increase of the base concentration and reaction temperature promoted the hydrogenation of the ester moiety. Thus, the hydrogenation of γ-keto ester **1a** with the Ru complex **5b** (S/C = 500, 8 atm H_2) in ethanol containing *t*-C_4H_9OK (10 mM) at 80°C in 2 h afforded the 1,4-diol **4a** in 20% yield and 98% *ee* (entry 1). The diol **4a** was

Table 2. Asymmetric hydrogenation of γ-keto ester **1a** into the diol **4a**.[a]



Entry	[base][b]	H_2 [atm]	*T* [°C]	*t* [h]	Yield [%][c], *ee* [%][d]		
					2b	**3a**	**4a**
1	10	8	80	2	41, 96	39, 97	20, 98
2	30	8	80	2	<1, nd	<1, nd	95, 91
3	50	8	40	24	9, 95	16, 95	74, 98
4	50	20	40	24	<1, nd	<1, nd	97, 97[e]
5	100	8	25	24	1, 92	13, 92	86, 97
6	100	8	40	16	<1, nd	<1, nd	>99, 97[f]

[a] Unless otherwise stated, reactions were conducted using 0.47–0.87 mmol of γ-keto ester **1a** in ethanol containing Ru complex (*S*,*S*)-**5b** and *t*-C_4H_9OK. **1a**/**5b** = 500:1. Complete conversion of **1a** was observed. No *tert*-butyl ester **2a** was detected. [b] Concentration of *t*-C_4H_9OK [mM] in the reaction mixture. [c] Determined by ^1H NMR analysis. [d] Determined by HPLC analysis on a chiral stationary phase. The *ee* value of **4a** was determined after conversion to the diacetate. nd: not determined. [e] 97% isolated yield, 97.2% *ee*. [f] 98% isolated yield, 96.6% *ee*.

obtained as a sole product when the concentration of base was increased to 30 mM, but the *ee* value of **4a** was decreased to 91% due to racemization of the product and the intermediates (entry 2). As a result of screening of the reaction conditions (entries 3–6), two sets of conditions quantitatively affording the diol **4a** in 97% *ee* within 24 h were found: 1) 50 mM of *t*-C_4H_9OK at 40°C under 20 atm of H_2 (entry 4) and 2) 100 mM of *t*-C_4H_9OK at 40°C under 8 atm of H_2 (entry 6). Thus, the DIPSkewphos/3-AMIQ–Ru(II) catalyst precisely controls chemoselectivity in the hydrogenation of γ-keto ester **1a**, affording either the hydroxy ester **2a** (including the lactone **3a**) or the 1,4-diol **4a** in high *ee* merely by changing the reaction conditions.

We applied the chemo- and enantioselective hydrogenation with the Ru complex **5b** to a variety of keto ester substrates (Table 3). Two reaction conditions were chosen for these experiments: condition A (**5b**/*t*-C_4H_9OK = 1:3.5, 8 atm H_2, 25°C and then lactonization with *t*-C_4H_9OK in toluene at 25°C when it was necessary), and condition B ([*t*-C_4H_9OK] = 50 mM, 20 atm H_2, 40°C). Under condition A, the hydrogenation of aromatic γ-keto esters **1a**, **1c**–**1g** with various substitution patterns on the aromatic rings with an S/C of 500 was completed in 2 h, affording the lactones **3a**, **3c**–**3g** in 97–99% *ee* quantitatively after the lactonization (entries 1, 3, and 5–8). No diol products were observed in all cases. The reactions of **1a** and **1c** with an S/C of 5000 were completed in 5 h with maintenance of a high level of enantioselectivity (entries 2 and 4).

The δ- and ε-keto esters **6a** and **6b** were quantitatively converted to the hydroxy esters **7a** and **7b**, both in 99% *ee*, under the typical conditions without the lactonization (entries 9 and 10).[10] It is known that β-keto esters are difficult substrates to hydrogenate with the conventional BINAP/diamine–Ru(II)-type

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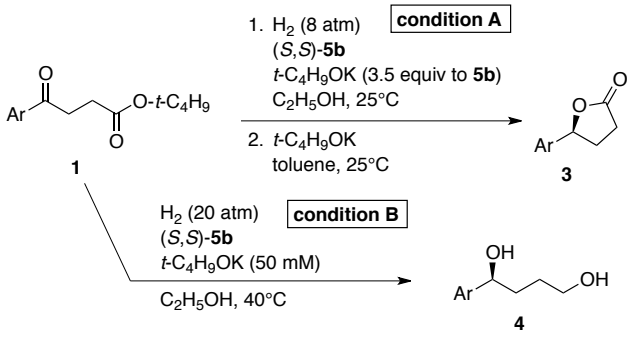
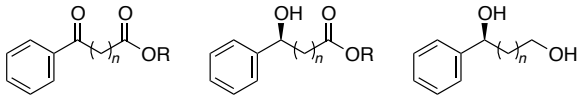
Table 3. Asymmetric hydrogenation of keto esters into the hydroxy esters or the diols.[a]



a: Ar = C_6H_5 **e**: Ar = 4-$CH_3OC_6H_4$
c: Ar = 2-$CH_3C_6H_4$ **f**: Ar = 2,5-$(CH_3O)_2C_6H_3$
d: Ar = 3,4-$(CH_3)_2C_6H_3$ **g**: Ar = 4-ClC_6H_4



6 **7** **8**

a: n = 3; R = t-C_4H_9 **b**: n = 4; R = t-C_4H_9 **c**: n = 1; R = C_2H_5

Entry	Condition	Substrate	S/C[b]	t [h]	Product: Yield [%][c], ee [%][d]
1	A	**1a**	500	2	**3a**: 96, 99(*S*)
2	A	**1a**[e]	5000	5	**3a**: 97, 97(*S*)
3	A	**1c**	500	2	**3c**: 96, 99(*S*)
4	A	**1c**[e]	5000	5	**3c**: 97, 99(*S*)
5	A	**1d**	500	2	**3d**: 96, 99
6	A	**1e**	500	2	**3e**: 97, 99(*S*)
7	A	**1f**	500	2	**3f**: 96, 99
8	A	**1g**	500	2	**3g**: 95, 97(*S*)
9	A[f]	**6a**	500	2	**7a**: 99, 99(*S*)
10	A[f]	**6b**	500	2	**7b**: 99, 99(*S*)
11	A[f,h]	**6c**[g]	500	24	**7c**: 99, 99(*S*)
12	B	**1a**	500	24	**4a**: 97, 97(*S*)
13	B[i]	**1a**[e]	5000	40	**4a**: 97, 96(*S*)
14	B	**1c**	500	24	**4c**: 95, 98(*S*)
15	B[i]	**1c**[e]	5000	40	**4c**: 97, 98(*S*)
16	B	**1d**	500	24	**4d**: 96, 97
17	B	**1e**	500	24	**4e**: 96, 97(*S*)
18	B	**1f**	500	24	**4f**: 96, 99
19	B	**1g**	500	24	**4g**: 96, 95(*S*)
20	B	**3a**[j]	500	24	**4a**: 98, 94(*S*)
21	B	**6a**	500	24	**8a**: 96, 98(*S*)
22	B	**6b**	500	24	**7b**: 89,[k,l] 96(*S*)
23	B	**6c**	500	24	**7c**: 88,[l,m] >99(*S*)

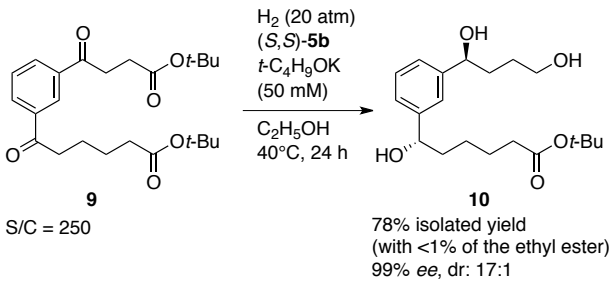
[a] Unless otherwise stated, reactions were conducted under condition A or B using 0.48–0.78 mmol of keto esters and Ru complex (*S*,*S*)-**5b** and t-C_4H_9OK. Complete conversion was observed. [b] Substrate-to-catalyst (**5b**) molar ratio. [c] Isolated yield of the product. [d] Determined by HPLC analysis on a chiral stationary phase. The *ee* value of **4a** was determined after conversion to the diacetate. [e] 4.7–5.2 mmol scale reaction. [f] The cyclization process (condition A, step 2) was not employed. [g] Keto form/enol form = 79:21. [h] Reaction under 20 atm of H_2. [j] Reaction under 50 atm of H_2. [j] (*S*)-**3a** in 96% *ee* was used. [k] 9% of the ethyl ester was obtained. [l] Diols **8b** and **8c** were not detected. [m] 12% of ethyl 3-phenyl-2-propenoate was obtained.

catalysts.[9a] The diamine ligands seemed to be replaced with the strongly chelating substrates on the metal center. Fortunately, this problem was solved by using the Ru complex **5b**. A β-keto ester **6c** (keto form/enol form = 79:21) was quantitatively hydrogenated under the modified condition A (20 atm H_2) to afford the hydroxy ester **7c** in 99% *ee* (entry 11).[11]

When hydrogenation of γ-keto esters **1a**, **1c**–**1g** with an S/C of 500 was carried out under condition B, the diols **4a**, **4c**–**4g** in 95–99% *ee* were obtained quantitatively in 24 h (entries 12, 14, and 16–19). Keto esters **1a** and **1c** were quantitatively converted to the diols under the modified condition B (50 atm of H_2) at an S/C of 5000 in 40 h without losing the enantioselectivity (entries 13 and 15).

The δ-keto ester **6a** was also predominantly hydrogenated into the 1,5-diol **8a** in 98% *ee* under condition B (entry 21). Notably, the ε-keto ester **6b** was converted to the hydroxy ester **7b** in 96% *ee* accompanied with the ethyl ester under condition B (entry 22). The hydrogenation of β-keto esters **6c** also afforded the hydroxy ester **7c** as a major product (entry 23). The diol products **8b** and **8c** were not observed in either of these cases. These results suggested that the 1,4- and 1,5-diols **4** and **8a** were obtained through the reduction of reversibly formed γ- and δ-lactones. In fact, the γ-lactone **3a** in 96% *ee* was smoothly hydrogenated to the 1,4-diaol **4a** in 94% *ee* under condition B (entry 20).[12]

We applied the DIPSkewphos/3-AMIQ–Ru(II) catalyst system to the enantioselective and ester regio (position)-selective hydrogenation of a γ-ε-diketo diester **9** (Scheme 2). The reaction conducted under condition B with an S/C of 250 was completed within 24 h to afford the tri-hydroxy ester **10** (including <1% of the ethyl ester) in 99% *ee* with a diastereomeric ratio of 17:1. The relatively low isolated yield of 78% was due to strong adsorption of the triol **10** on the SiO_2 column. As we expected, no hydrogenation of the ester group at the ε-keto ester moiety was observed, in contrast to complete reduction of the γ-keto ester moiety.



Scheme 2. Enantioselective and ester regioselective hydrogenation of a γ-ε-diketo ester **9**.

In conclusion, we reported herein chemo- and enantioselective hydrogenation of aromatic γ- and δ-keto esters with a newly devised DIPSkewphos/3-AMIQ–Ru(II) catalyst system. Under the optimized conditions (condition A) the γ- and δ-hydroxy esters (including γ-lactones) were obtained in 97%–99% *ee* quantitatively. On the other hand, the 1,4- and 1,5-diols were predominantly obtained in 95%–99% *ee* under the slightly harsh conditions (condition B). The results were reproducible for

the reactions with S/Cs of 500 and 5000. Thus, the chemoselectivity producing hydroxy esters or diols was precisely controlled just by changing the reaction conditions. The reactivity of the ester group was significantly dependent on the length of the carbon-spacer between the two carbonyl moieties. The reaction of β- and ε-keto esters under both conditions selectively afforded the hydroxy esters. The enantioselective and ester regio (position)-selective hydrogenation of a γ-ε-diketo diester into the tri-hydroxy ester was also achieved.

Acknowledgements

We thank Dr. T. Katayama and Mr. N. Utsumi at Kanto Chemical Co., Inc. for useful discussion on production of the DIPSkewphos/3-AMIQ–Ru(II) complex. This work was supported by a Grant-in-Aid from the Japan Society for the Promotion of Science (JSPS) (No. 15H03802) and a grant from the MEXT (Japan) program "Strategic Molecular and Materials Chemistry through Innovative Coupling Reactions" of Hokkaido University.

Keywords: asymmetric catalysis • chemoselectivity • hydrogenation • keto esters • ruthenium

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10.1002/anie.201711363

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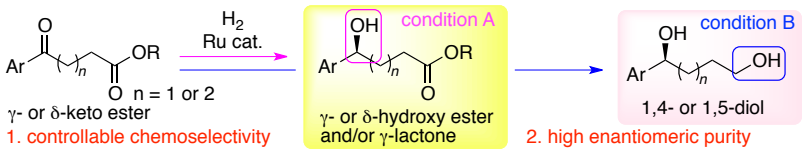

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Chemoselectivity Control in the Asymmetric Hydrogenation of γ- and δ-Keto Esters into the Hydroxy Esters or the Diols

Chemoselectivity in the asymmetric hydrogenation of γ- and δ-keto esters into the hydroxy esters (including the lactones) or the diols catalyzed by the novel DIPSkewphos/3-AMIQ–Ru(II) complex was precisely controlled just by changing the reaction conditions. The enantiomeric purity of both products was very high (95%–99% *ee*). The β- and ε-keto esters were selectively converted to the hydroxy esters regardless of the reaction conditions.