

Supplementary Information

Solvent selection based on the conceptual process design with combining cost evaluation and life cycle assessments for developing new reaction pathways

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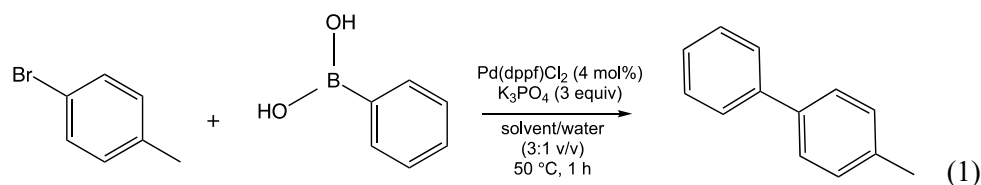
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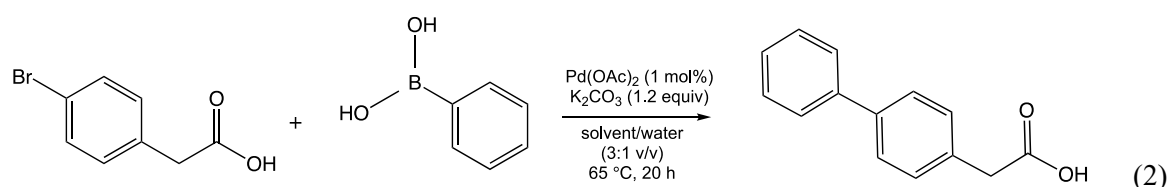
The model processes for solvent selection were designed based on the synthetic procedure in the previous literature.¹ The synthetic procedure for Reactions 1–3 is as follows:

Reaction 1:



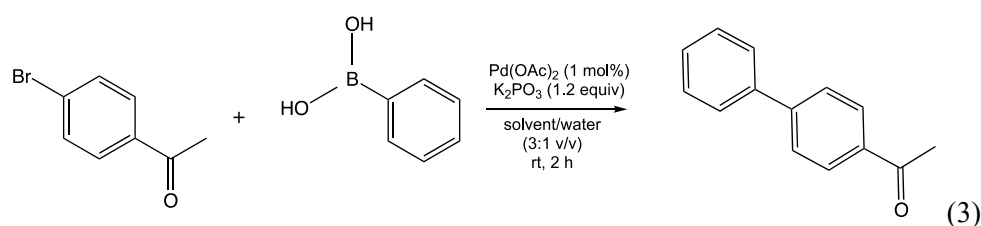
4-bromotoluene (0.103 g), phenylboronic acid (0.0878 g), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)-DCM complex (0.0196 g), potassium phosphate (0.382 g) were added to water (0.6 ml) and the chosen solvent (1.8 ml). The reaction mixture was stirred for 1 hours at 323 K, and then diluted with diethyl ether (DEE) (20 ml) and washed with water (3 × 20 ml). 4-Phenyltoluene was obtained from the organic phase.

Reaction 2:



4-bromophenyl acetic acid (0.129 g), phenylboronic acid (0.0878 g), palladium acetate (0.0013 g), potassium carbonate (0.0995 g) were added to water (0.6 ml) and the chosen solvent (1.8 ml). The reaction mixture was stirred for 20 hours at 338 K, and then allowed to cool to the ambient temperature. The reaction mixture was diluted with water (10 ml), acidified with hydrochloric acid to produce a precipitate, and extracted with dichloromethane (CL2M) (2 × 15 ml). 4-Biphenylacetic acid was obtained from the organic phase.

Reaction 3:



4-bromoacetophenone (0.119 g), phenylboronic acid (0.0878 g), palladium acetate (0.0013 g), and potassium carbonate (0.0995 g) were added to water (0.6 ml) and the chosen solvent (1.8 ml). The reaction mixture was stirred for 2 hours at the ambient temperature, and then diluted with DEE (20 ml) and washed with water (2 × 20 ml). Biphenyl methyl ketone was obtained from the organic phase.

The conversion from bromoarene to biphenyl product are summarized in Table S1.¹

Table S1 Conversion from bromoarene to biphenyl product in three reactions of Suzuki-Miyaura coupling.¹

Reaction solvent	Reaction 1	Reaction 2	Reaction 3
NMP	0.85	0.98	1
Toluene	0.94	1	0.42
MEK	0.92	0.92	0.30
IPA	0.81	1	1
EtAc	0.76	1	0.28

The parameters for the evaluation of the production cost are summarized in Table S2.

Table S2 Parameters for cost evaluation.

Parameter	Price	Unit
<i>Solvent</i> ²		
NMP	2.39	USD/kg
Toluene	0.468	USD/kg
MEK	1.10	USD/kg
IPA	0.956	USD/kg
EtAc	0.889	USD/kg
DEE	2.31	USD/kg
CL2M	0.448	USD/kg
<i>Utility</i> ^{3,4}		
Low-pressure steam	15.2	USD/GJ
High-pressure steam	18.9	USD/GJ
Electricity	0.182	USD/kWh
Cooling water	0.354	USD/GJ
Refrigerated water	4.40	USD/GJ

The CO₂ emission factors of the solvents (i.e., NMP, Toluene, MEK, IPA, EtAc, and CL2M) and utilities (i.e., low-pressure steam and electricity) were mainly obtained from IDEA database.⁵ For the solvent DEE, high-pressure steam and chilled water, which are not included in the database, the approximate values of 2.87 kg-CO₂/kg DEE, 0.214 kg CO₂/MJ and 0.054 kg-CO₂/MJ were estimated (based on process simulation and average Japanese electricity grid's CO₂ emission factor) and applied, respectively.

The results of process simulation in System 3 of Reactions 1–3 are summarized in Table S3.

Table S3 Results of process simulation in System 3 of Reactions 1–3.

Parameter	Reaction solvent				
	NMP	Toluene	MEK	IPA	EtAc
<i>Reaction 1</i>					
Purity of recycled reaction solvent [wt%]	99.0	99.9	99.0	99.7	99.5
Recovery ratio of recycled reaction solvent [-]	0.995	0.995	0.965	0.953	0.991
Purity of recycled DEE [wt%]	98.6	98.7	98.7	98.6	98.0
Recovery ratio of recycled DEE [-]	0.981	0.990	0.990	0.990	0.990
Number of stages of T2 [-]	2	8	15	9	11
Number of stages of T3 [-]	4	–	21	6	5
Number of stages of T4 [-]	–	–	20	2	–
<i>Reaction 2</i>					
Purity of recycled reaction solvent [wt%]	99.3	99.6	99.7	99.8	99.9
Recovery ratio of recycled reaction solvent [-]	0.996	1	0.998	0.960	0.998
Purity of recycled CL2M [wt%]	99.7	99.7	99.7	98.3	99.3
Recovery ratio of recycled CL2M [-]	0.990	0.990	0.990	1	0.990
Number of stages of T2 [-]	2	10	14	22	13
Number of stages of T3 [-]	7	–	–	2	–
Number of stages of T4 [-]	–	–	–	9	–
Number of stages of T5 [-]	–	–	–	8	–
Number of stages of T6 [-]	–	–	–	5	–
<i>Reaction 3</i>					
Purity of recycled reaction solvent [wt%]	99.0	99.9	99.0	99.7	99.5
Recovery ratio of recycled reaction solvent [-]	0.995	0.999	0.965	0.956	0.991
Purity of recycled DEE [wt%]	98.6	98.7	98.7	98.6	98.0
Recovery ratio of recycled DEE [-]	0.981	0.990	0.990	0.990	0.990
Number of stages of T2 [-]	2	8	14	9	11
Number of stages of T3 [-]	4	–	20	6	5
Number of stages of T4 [-]	–	–	24	2	–

Figs. S1–S14 show the process flow of the waste solvent distillation in System 3 of Reactions 1–3.

Fig. S1 shows the process flow of System 3 when NMP is used as the reaction solvent in Reaction 1. The waste solvent flowing out of K1 contains NMP, water, and DEE. The distillation column (T2) first separated the DEE. The cooler (E4) then cooled the DEE, which was recovered from the top of T2, and the recovered DEE was returned to T1 with the make-up. The bottom stream containing NMP and small amount of water from T2 was fed to the distillation column (T3). In addition, to achieve solvent recovery requirements, the raffinate stream from T1 was also fed to the T3. NMP is recovered from the bottom stream of T3 because the boiling point of NMP is higher than that of water. Assuming removal of trash in the raffinate, we set that the bottom stream from T3 was vaporized by the evaporator (K2). Then, the vapor was cooled to reaction temperature (E9) before being recycled to the reactor.

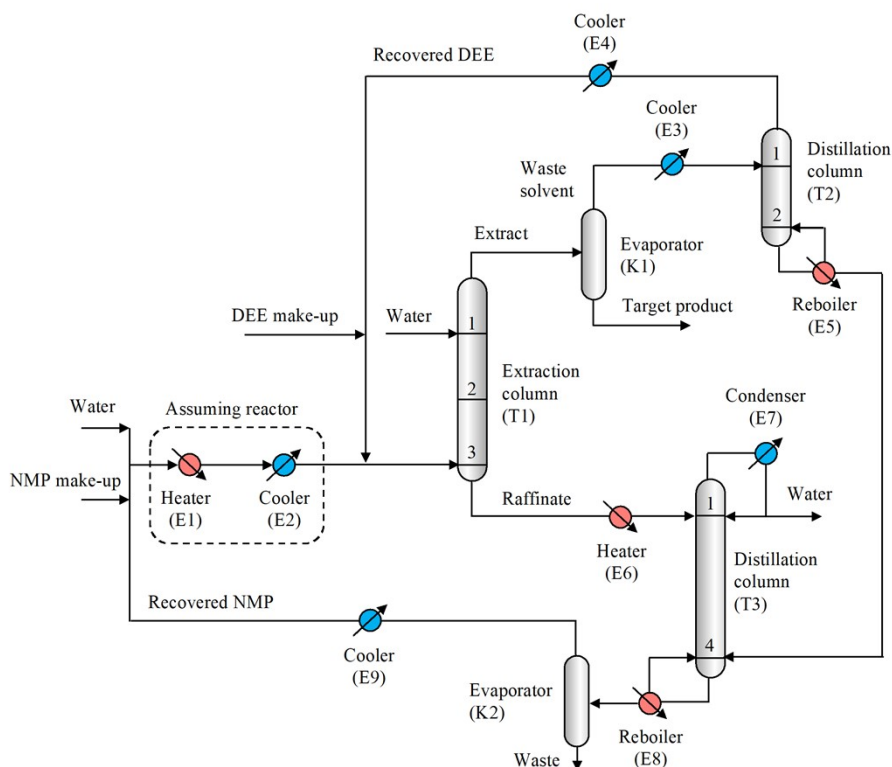


Fig. S1 Process flow of System 3 when NMP is used as the reaction solvent in Reaction 1.

Fig. S2 shows the process flow of System 3 when toluene is used as the reaction solvent in Reaction 1. The waste solvent flowing out of K1 contains toluene and DEE. The distillation column (T2) separated the DEE. The cooler (E5) then cooled the DEE, which was recovered from the top of T2, and the recovered DEE was returned to T1 with the make-up. The bottom stream from T2 is high purity toluene because water is only a small fraction of the extract stream of T1. The bottom stream from T2 was cooled to reaction temperature (E7) before being recycled to the reactor.

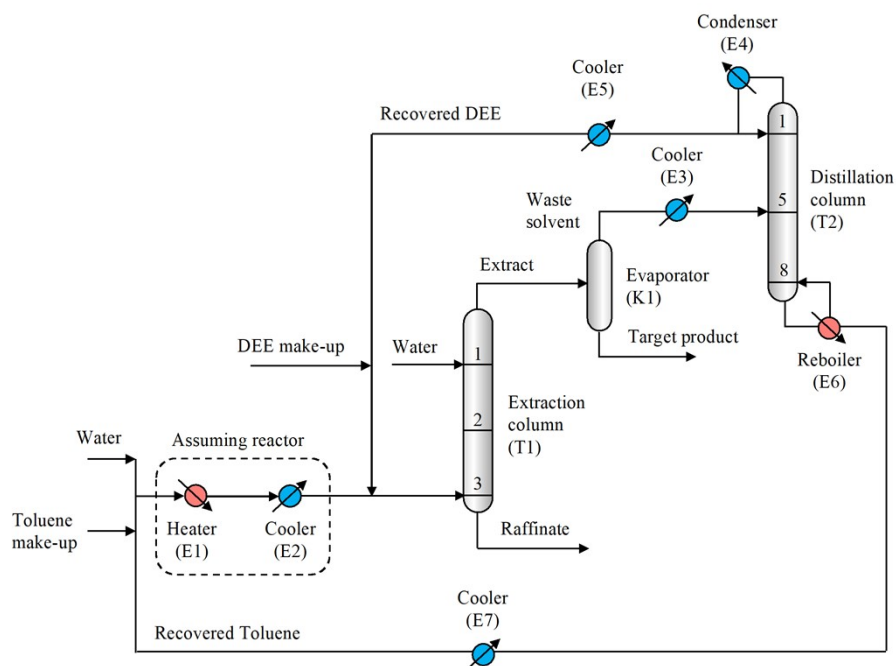


Fig. S2 Process flow of System 3 when toluene is used as the reaction solvent in Reaction 1.

Fig. S3 shows the process flow of System 3 when MEK is used as the reaction solvent in Reaction 1. The waste solvent flowing out of K1 contains MEK, water, and DEE. The distillation column (T2) first separated the DEE. The cooler (E5) then cooled the DEE, which was recovered from the top of T2, and the recovered DEE was returned to T1 with the make-up. The bottom stream containing MEK and water from T2 was fed to the distillation column (T3). The mixed solution of MEK and water exhibits an azeotropic phenomenon; thus, achieving high recovery of high-purity MEK is impossible using only T3. An azeotropic distillation method was used with an entraining agent. Toluene was used as an entrainer.⁶ The vapor exiting the top of T3 near the azeotropic phenomenon was fed to the condenser (E7) and then sent to the decanter (V1). The condensate was separated in liquid-liquid into the organic phase and the aqueous phase. The aqueous phase was recovered from V1 and the organic phase was returned to upper part of T3 as reflux. The bottom stream of T3 was fed to the distillation column (T4). MEK was recovered from the distillate stream of T4 and cooled to reaction temperature (E10) before being recycled to the reactor. The bottom stream of T4 mainly toluene was returned to V1.

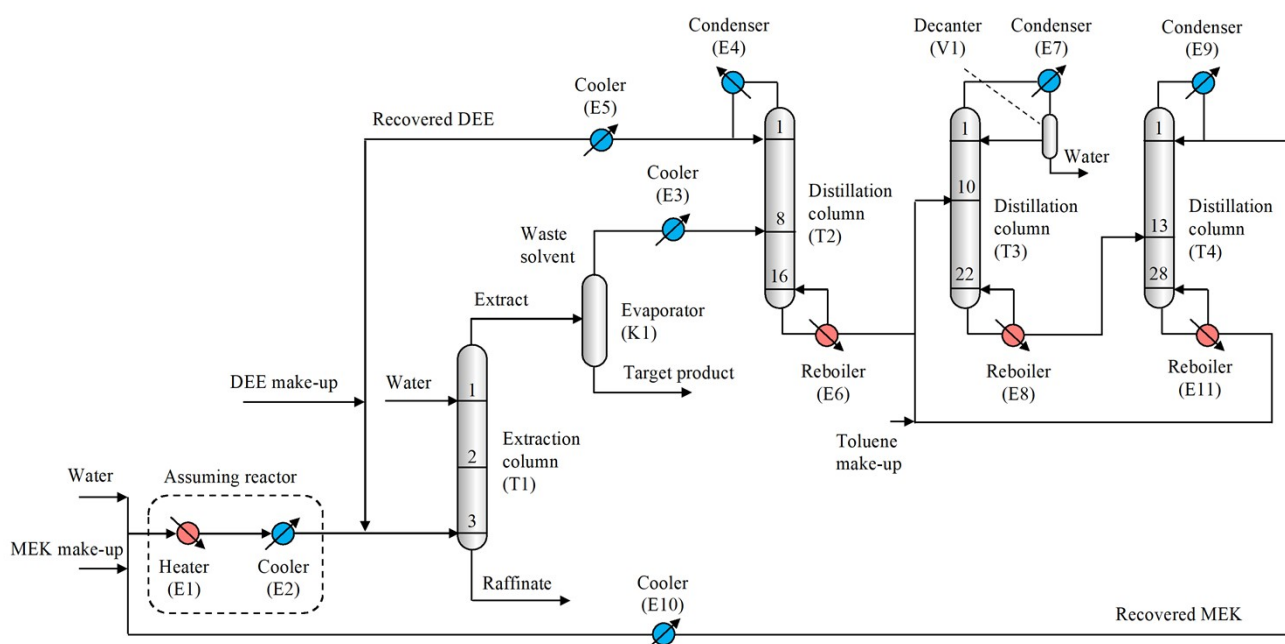


Fig. S3 Process flow of System 3 when MEK is used as the reaction solvent in Reaction 1.

Fig. S4 shows the process flow of System 3 when EtAc is used as the reaction solvent in Reaction 1. The waste solvent flowing out of K1 contains EtAc, water, and DEE. The distillation column (T2) first separated the DEE. The cooler (E5) then cooled the DEE, which was recovered from the top of T2, and the recovered DEE was returned to T1 with the make-up. The bottom stream containing EtAc and water from T2 was fed to the distillation column (T3). The mixed solution of EtAc and Water exhibits a liquid-liquid separation. The vapor exiting the top of T3 was condensed and then fed to the decanter (V1).⁷ The condensate was separated in liquid-liquid into an organic phase and an aqueous phase. The aqueous phase was recovered from V1 and the organic phase was returned to the upper part of T3 as reflux. EtAc was recovered from the bottom stream of T3 and cooled to reaction temperature (E9) before being recycled to the reactor.

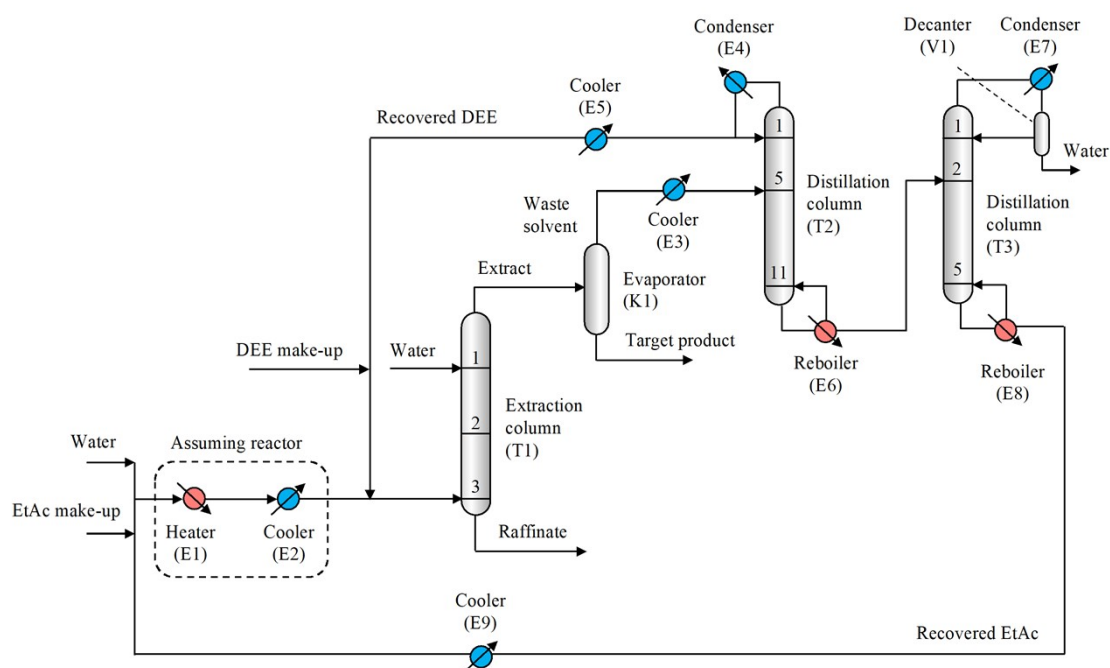


Fig. S4 Process flow of System 3 when EtAc is used as the reaction solvent in Reaction 1.

Fig. S5 shows the process flow of System 3 when NMP is used as the reaction solvent in Reaction 2. The waste solvent flowing out of from K1 contains NMP and CL2M. The distillation column (T2) first separated the CL2M. The cooler (E5) then cooled the CL2M, which was recovered from the top of T2, and the recovered CL2M was returned to T1 with the make-up. The bottom stream from T2 is high purity NMP because water is only a small fraction of the extract stream of T1. In addition, to achieve solvent recovery requirements, the raffinate stream from T1 was fed to the T3. NMP is recovered from the bottom stream of T3 because the boiling point of NMP is higher than that of water. The bottom stream from T2 and T3 was cooled to reaction temperature (E9) before being recycled to the reactor.

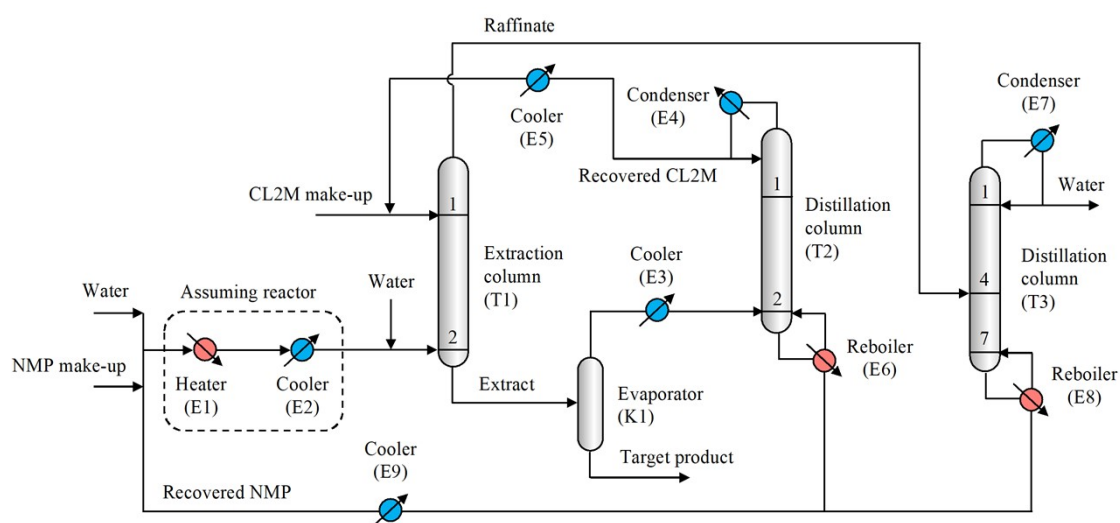


Fig. S5 Process flow of System 3 when NMP is used as the reaction solvent in Reaction 2.

Fig. S6 shows the process flow of System 3 when toluene is used as the reaction solvent in Reaction 2. The waste solvent flowing out of K1 contains toluene and CL2M. The distillation column (T2) separated the CL2M. The cooler (E5) then cooled the CL2M, which was recovered from the top of T2, and the recovered CL2M was returned to T1 with the make-up. The bottom stream from T2 is high purity toluene because water is only a small fraction of the extract stream of T1. The bottom stream from T2 was cooled to reaction temperature (E7) before being recycled to the reactor.

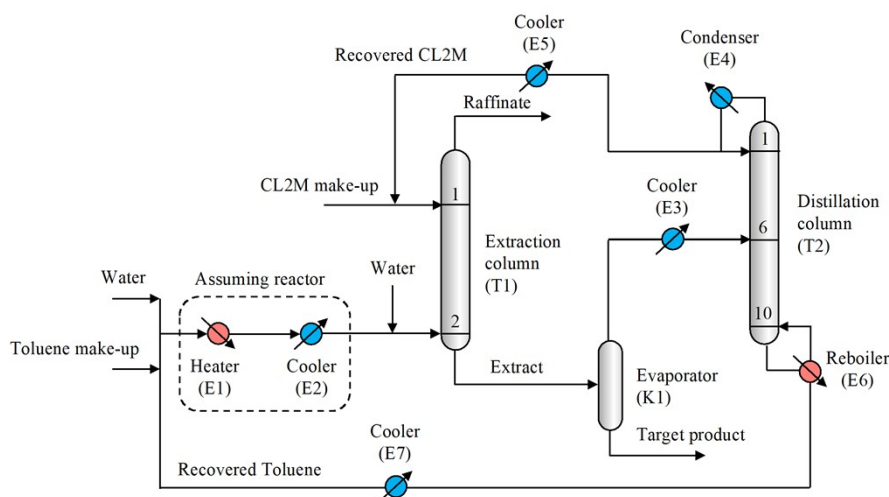


Fig. S6 Process flow of System 3 when toluene is used as the reaction solvent in Reaction 2.

Fig. S7 shows the process flow of System 3 when MEK is used as the reaction solvent in Reaction 2. The waste solvent flowing out of K1 contains MEK and CL2M. The distillation column (T2) separated the CL2M. The cooler (E5) then cooled the CL2M, which was recovered from the top of T2, and the recovered CL2M was returned to T1 with the make-up. The bottom stream from T2 is high purity MEK because water is only a small fraction of the extract stream of T1. The bottom stream from T2 was cooled to reaction temperature (E7) before being recycled to the reactor.

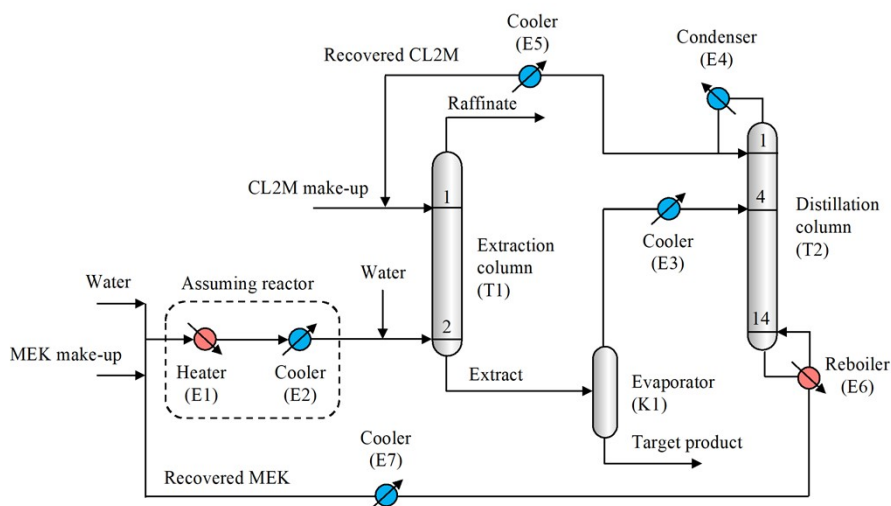


Fig. S7 Process flow of System 3 when MEK is used as the reaction solvent in Reaction 2.

Fig. S8 shows the process flow of System 3 when IPA is used as the reaction solvent in Reaction 2. The waste solvent flowing out of from K1 contains IPA and CL2M. The distillation column (T2) separated the CL2M. The cooler (E5) then cooled the CL2M, which was recovered from the top of T2, and the recovered CL2M was returned to T1 with the make-up. The bottom stream from T2 is high purity IPA because water is only a small fraction of the extract stream of T1. In addition, to achieve solvent recovery requirements, the raffinate stream containing IPA, water, and CL2M from T1 was also fed to the T3. The distillation column (T3) separated the CL2M. The cooler (E5) then cooled the CL2M. The bottom stream containing IPA and water from T3 was fed to the distillation column (T4). The mixed solution of IPA and water exhibits an azeotropic phenomenon; thus, achieving high recovery of high-purity IPA is impossible using only T4. An azeotropic distillation method was used with an entraining agent.⁸ Cyclohexane (CH) was used as an entrainer.⁹ The water was recovered from the bottom stream of T4. The vapor exiting the top of T4 near the azeotropic phenomenon was fed to the distillation column (T5). IPA was recovered from the bottom stream of T5. IPA from the bottom stream of T2 and T5 was cooled to reaction temperature (E7) before being recycled to the reaction process. The vapor exiting the top of T5 near the azeotropic phenomenon was fed to the condenser (E11) and then sent to the decanter (V1). The condensate was separated in liquid–liquid into the organic phase and the aqueous phase. The organic phase was returned to the upper part of T5 as reflux. The aqueous phase was fed to the distillation column (T6). The water was recovered from the bottom stream of T6. The vapor exiting the top of T6 near the azeotropic phenomenon was cooled by E13 and then returned to T5.

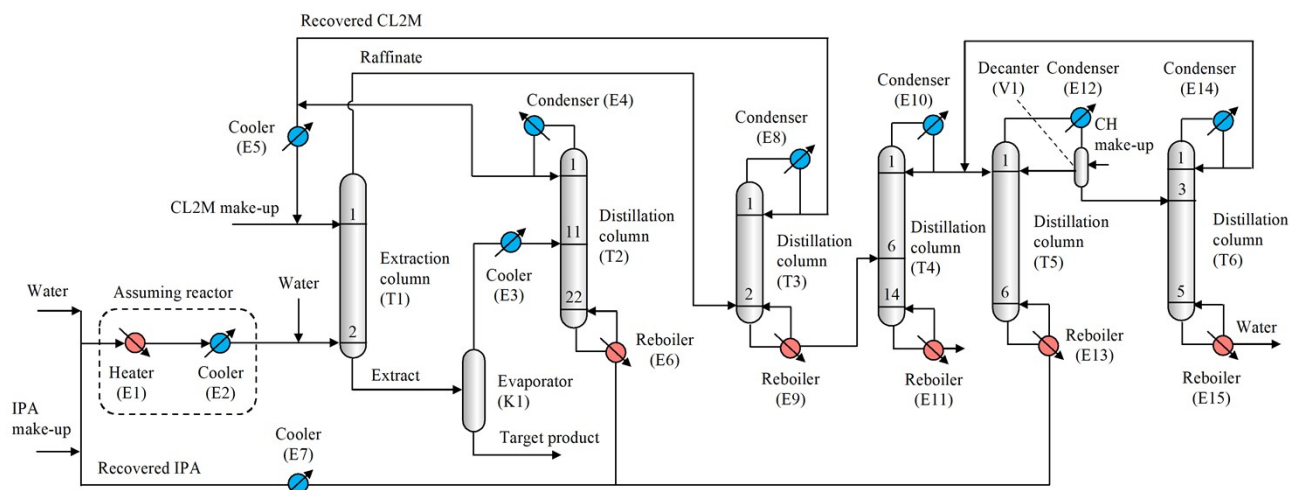


Fig. S8 Process flow of System 3 when IPA is used as the reaction solvent in Reaction 2.

Fig. S9 shows the process flow of System 3 when EtAc is used as the reaction solvent in Reaction 2. The waste solvent flowing out of K1 contains EtAc and CL2M. The distillation column (T2) separated the CL2M. The cooler (E5) then cooled the CL2M, which was recovered from the top of T2, and the recovered CL2M was returned to T1 with the make-up. The bottom stream from T2 is high purity EtAc because water is only a small fraction of the extract stream of T1. The bottom stream from T2 was cooled to reaction temperature (E7) before being recycled to the reactor.

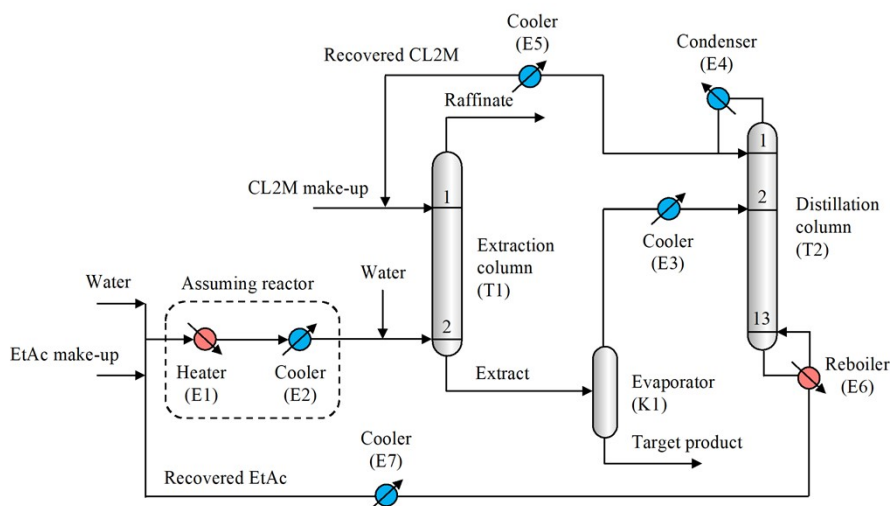


Fig. S9 Process flow of System 3 when EtAc is used as the reaction solvent in Reaction 2.

Fig. S10 shows the process flow of System 3 when NMP is used as the reaction solvent in Reaction 3. The waste solvent flowing out of K1 contains NMP, water, and DEE. The distillation column (T2) first separated the DEE. The cooler (E4) then cooled the DEE, which was recovered from the top of T2, and the recovered DEE was returned to T1 with the make-up. The bottom stream containing NMP and small amount of water from T2 was fed to the distillation column (T3). In addition, to achieve solvent recovery requirements, the raffinate stream from T1 was also fed to the T3. NMP is recovered from the bottom stream of T3 because the boiling point of NMP is higher than that of water. Assuming removal of trash in the raffinate, we set that the bottom stream from T3 was vaporized by the evaporator (K2). Then, the vapor was cooled to reaction temperature (E9) before being recycled to the reactor.

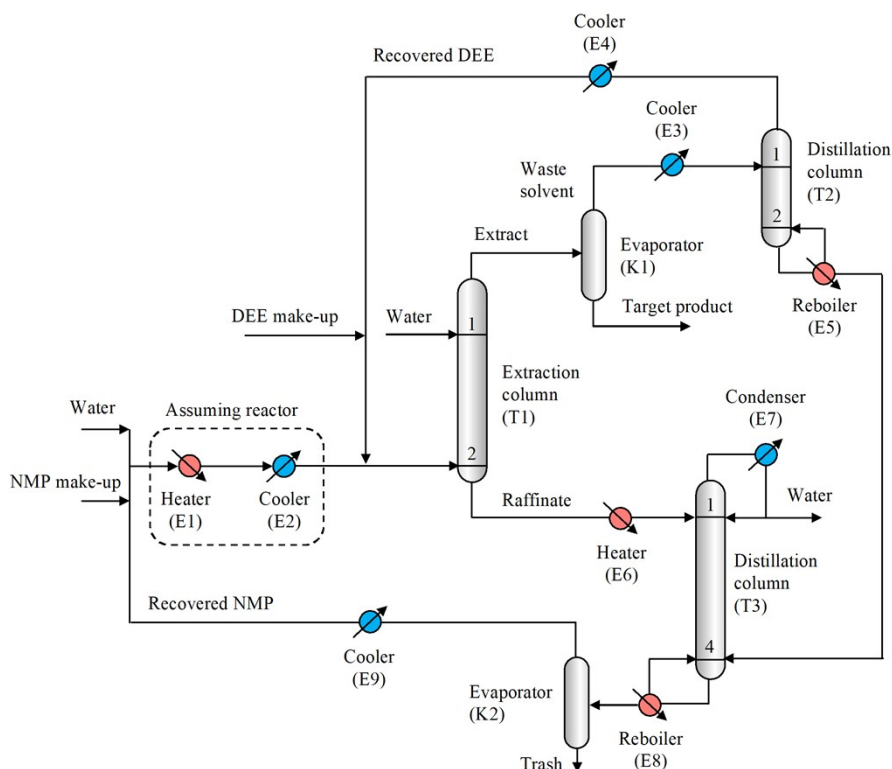


Fig. S10 Process flow of System 3 when NMP is used as the reaction solvent in Reaction 3.

Fig. S11 shows the process flow of System 3 when toluene is used as the reaction solvent in Reaction 3. The waste solvent flowing out of K1 contains toluene and DEE. The distillation column (T2) separated the DEE. The cooler (E5) then cooled the DEE, which was recovered from the top of T2, and the recovered DEE was returned to T1 with the make-up. The bottom stream from T2 is high purity toluene because water is only a small fraction of the extract stream of T1. The bottom stream from T2 was cooled to reaction temperature (E7) before being recycled to the reactor.

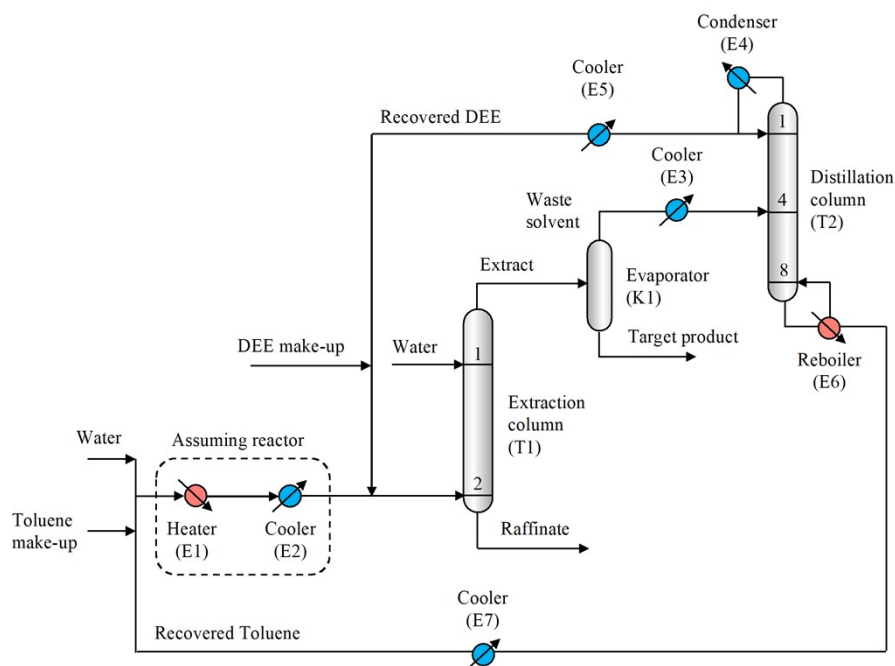


Fig. S11 Process flow of System 3 when toluene is used as the reaction solvent in Reaction 3.

Fig. S12 shows the process flow of System 3 when MEK is used as the reaction solvent in Reaction 3. The waste solvent flowing out of K1 contains MEK, water, and DEE. The distillation column (T2) first separated the DEE. The cooler (E5) then cooled the DEE, which was recovered from the top of T2, and the recovered DEE was returned to T1 with the make-up. The bottom stream containing MEK and water from T2 was fed to the distillation column (T3). The mixed solution of MEK and water exhibits an azeotropic phenomenon; thus, achieving high recovery of high-purity MEK is impossible using only T3. An azeotropic distillation method was used with an entraining agent. Toluene was used as an entrainer.⁶ The vapor exiting the top of T3 near the azeotropic phenomenon was fed to the condenser (E7) and then sent to the decanter (V1). The condensate was separated in liquid-liquid into the organic phase and the aqueous phase. The aqueous phase was recovered from V1 and the organic phase was returned to upper part of T3 as reflux. The bottom stream of T3 was fed to the distillation column (T4). MEK was recovered from the distillate stream of T4 and cooled to reaction temperature (E10) before being recycled to the reactor. The bottom stream of T4 mainly toluene was returned to V1.

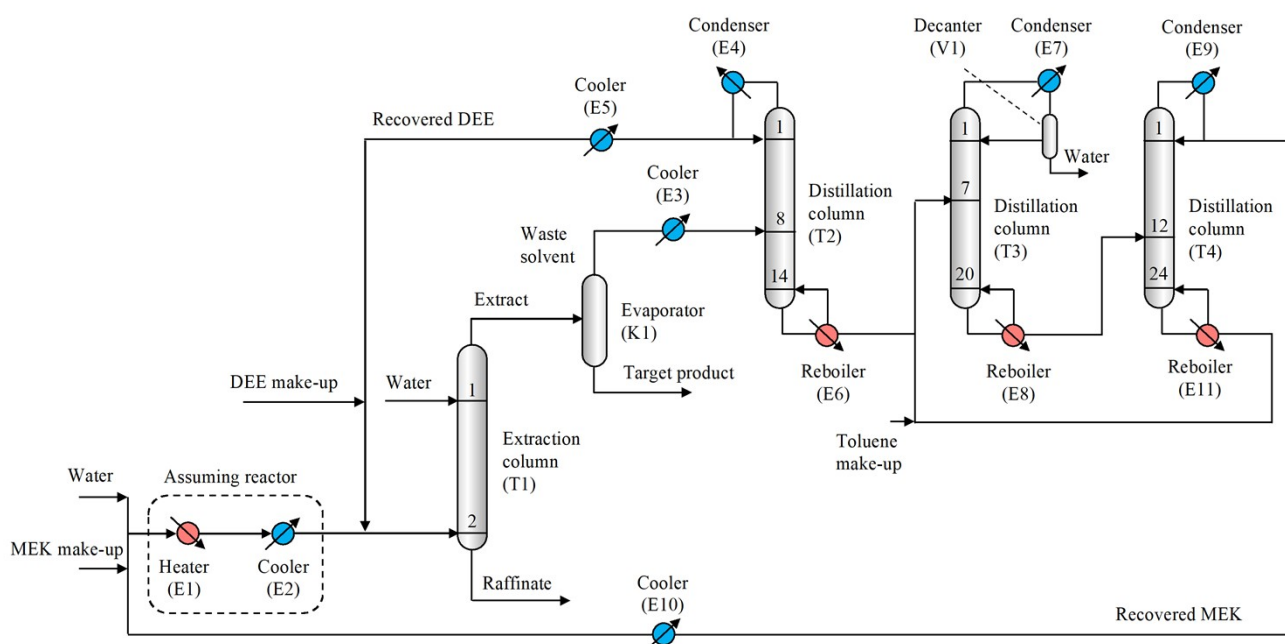


Fig. S12 Process flow of System 3 when MEK is used as the reaction solvent in Reaction 3.

Fig. S13 shows the process flow of System 3 when IPA is used as the reaction solvent in Reaction 3. The waste solvent flowing out of K1 contains IPA, water, and DEE. The distillation column (T2) first separated the DEE. The cooler (E5) then cooled the DEE, which was recovered from the top of T2, and the recovered DEE was returned to T1 with the make-up. The bottom stream containing IPA and water from T2 was fed to the distillation column (T3). The mixed solution of IPA and water exhibits an azeotropic phenomenon; thus, achieving high recovery of high-purity IPA is impossible using only T3. An azeotropic distillation method was used with an entraining agent.⁸ Cyclohexane (CH) was used as an entrainer.⁹ IPA was recovered from the bottom stream of T3 and cooled to reaction temperature (E10) before being recycled to the reaction process. The vapor exiting the top of T3 near the azeotropic phenomenon was fed to the condenser (E7) and then sent to the decanter (V1). The condensate was separated in liquid–liquid into the organic phase and the aqueous phase. The organic phase was returned to the upper part of T3 as reflux. The aqueous phase was fed to the distillation column (T4). The water was recovered from the bottom stream of T4. The vapor exiting the top of T4 near the azeotropic phenomenon was directed to E7 and then returned to V1. The lost CH from the bottom stream of T3 and T4 was routed to V1 as make-up.

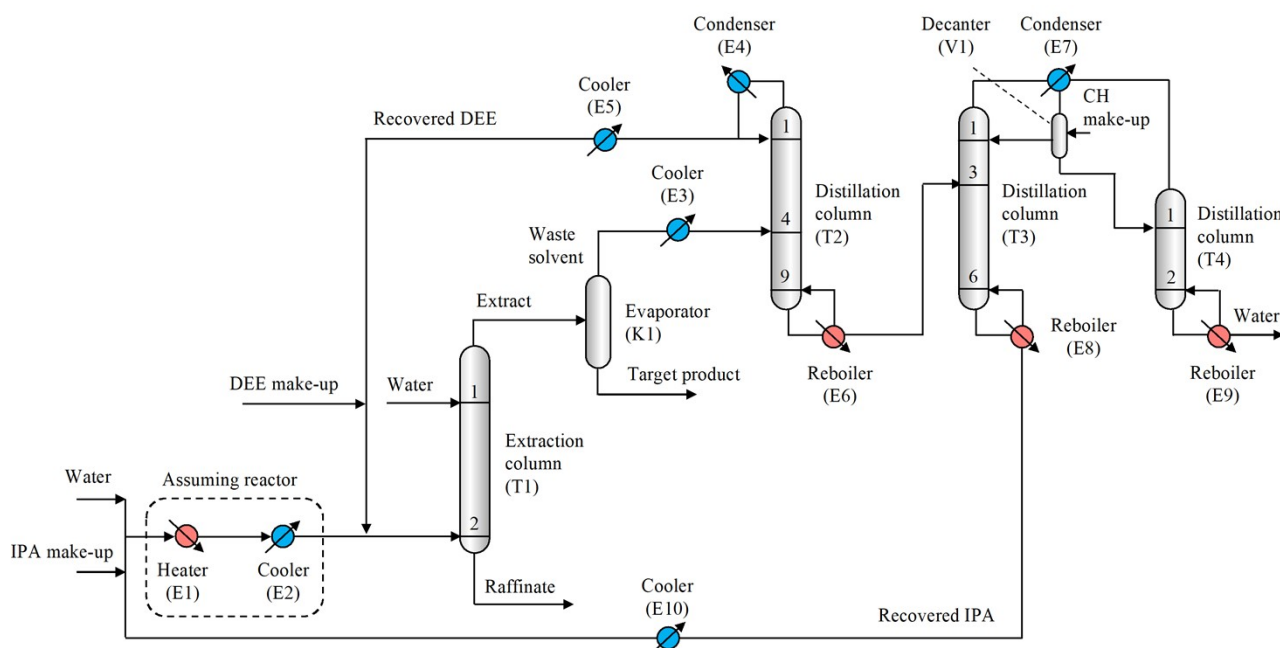


Fig. S13 Process flow of System 3 when IPA is used as the reaction solvent in Reaction 3.

Fig. S14 shows the process flow of System 3 when EtAc is used as the reaction solvent in Reaction 3. The waste solvent flowing out of K1 contains EtAc, water, and DEE. The distillation column (T2) first separated the DEE. The cooler (E5) then cooled the DEE, which was recovered from the top of T2, and the recovered DEE was returned to T1 with the make-up. The bottom stream containing EtAc and water from T2 was fed to the distillation column (T3). The mixed solution of EtAc and Water exhibits a liquid-liquid separation. The vapor exiting the top of T3 was condensed and then fed to the decanter (V1).⁷ The condensate was separated in liquid-liquid into an organic phase and an aqueous phase. The aqueous phase was recovered from V1 and the organic phase was returned to the upper part of T3 as reflux. EtAc was recovered from the bottom stream of T3 and cooled to reaction temperature (E9) before being recycled to the reactor.

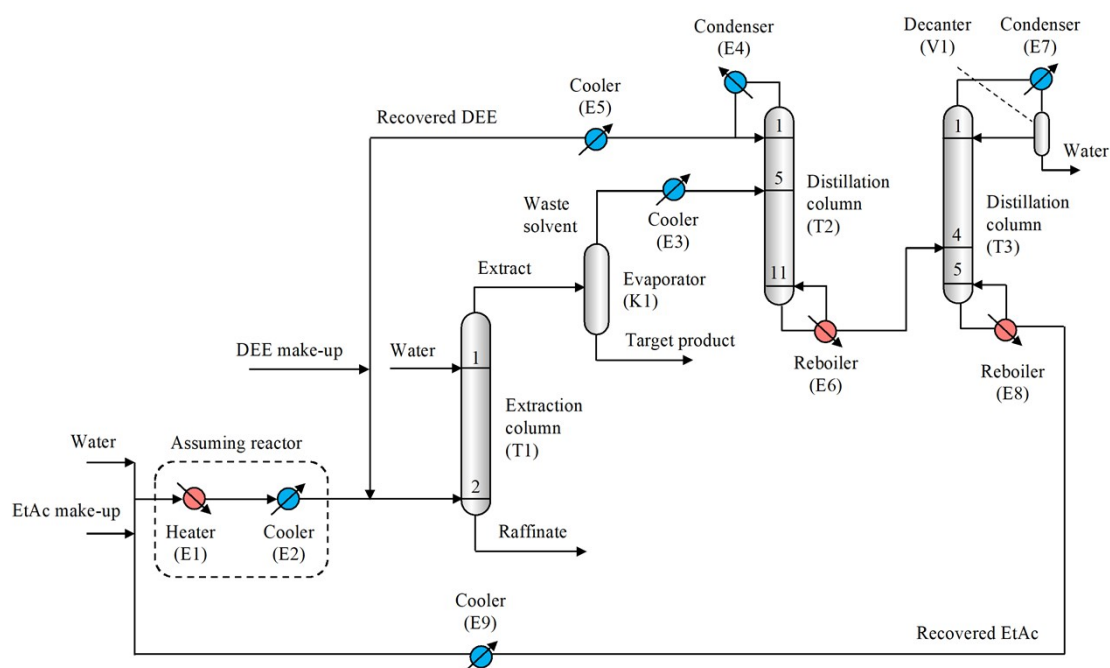


Fig. S14 Process flow of System 3 when EtAc is used as the reaction solvent in Reaction 3.

Fig. S15 shows the process flow of the waste solvent incineration.¹⁰ The waste solvent and air corresponding to the number of carbons in the waste solvent were fed to the incinerator, and the waste solvent was completely combusted at 1173 K. To make effective use of the waste heat, the combustion gases were used to produce a low-pressure steam after heat exchange with the mixture of the waste solvent and air. The minimum heat exchange temperature difference between the combustion gases and the low-pressure steam was set at 20 K. The low-pressure steams produced was used as a heat source in the chemical processes, and the excess low-pressure steam was assumed to be sold.

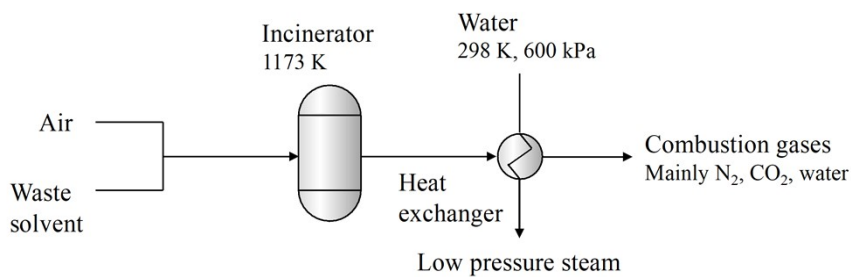


Fig. S15 Process flow of waste solvent incineration.

Fig. S16 shows the effect of the number of stages on the cost for the production when IPA is used as the reaction solvent. Here, The OPEX of each distillation column represents the steam cost calculated from the energy consumption of the reboiler. The CAPEX for each distillation column is the purchase price of the distillation column and trays divided by the payback periods (5 years). In T2 to T4, when the number of stages is small (*i.e.*, CAPEX), OPEX is large, and vice versa. This means that the appropriate design and operating conditions exist to minimize the costs for the production.

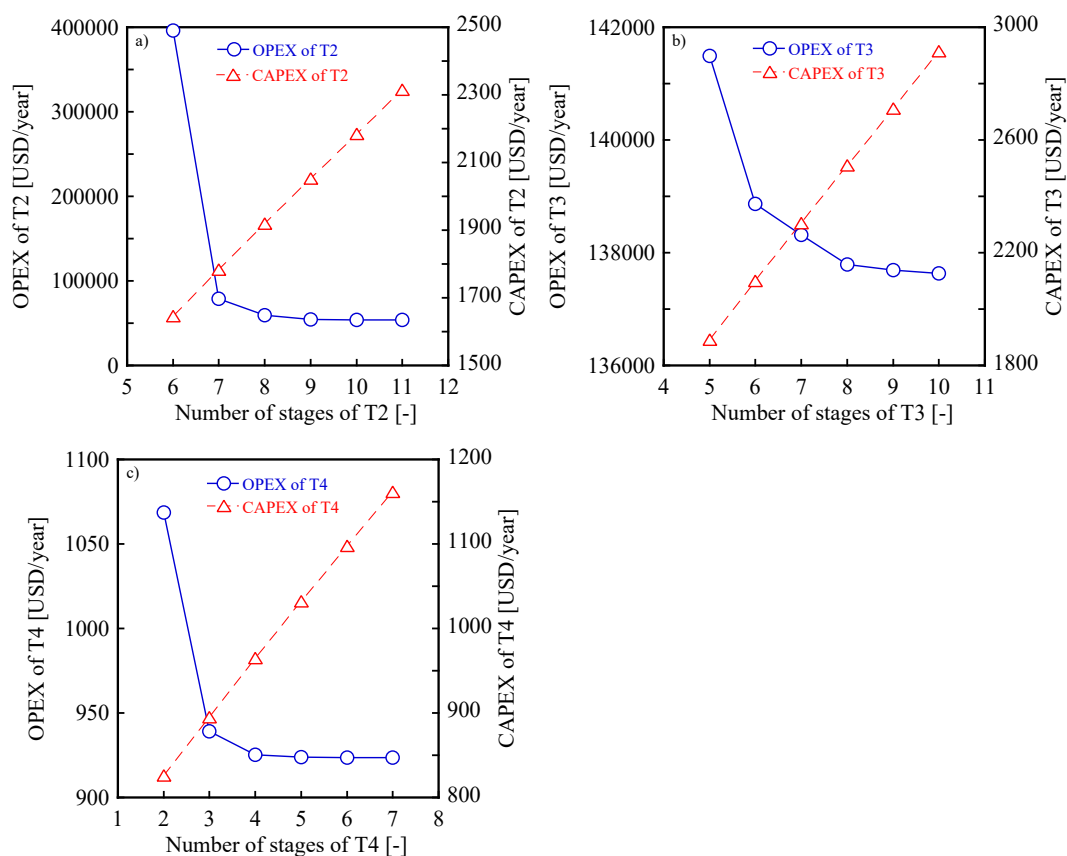


Fig. S16 Effect of number of stages from T2 to T4 on costs for System 3 when IPA was used as the reaction solvent in Reaction 1.

Fig. S17 shows the liquid-liquid equilibrium relationship for IPA/Water/DEE and Toluene/Water/DEE at 298 K. The liquid-liquid equilibrium relationships were calculated using the NRTL model with the parameters built into Pro/II.

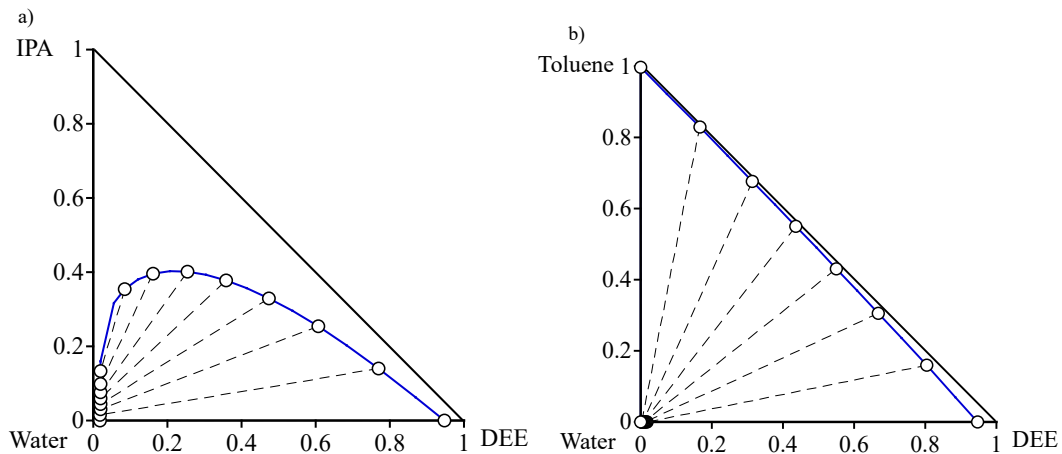


Fig. S17 Liquid-liquid equilibrium relationships at 298 K: a) IPA/Water/DEE, b) Toluene/Water/DEE.

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