

Index

a

- acetic anhydride (Ac₂O) 287–289, 291, 293, 295
- acetone-cyanohydrin (ACH) process 283
- 10-acetoxydecanoic acid 293
- Ackermann, L. 178–179, 181, 191–195
- active pharmaceutical ingredient (API) 10, 262
- Kumada–Corriu coupling 122
- micellar technology 230
- drug substance 23
- Buchwald–Hartwig amination
- NaTMT 46, 47
- Pd(dba)DPEPhos pre-catalyst 45–46
- scale-up and manufacturing 48
- screening condition formations 43–45
- solubility studies 50–53
- Chan–Lam coupling
- aerobic oxidation 32–35
- aerobic oxidation on scale 37–38
- Cu-catalyzed 29
- homogenous conditions 31–32
- oxidative coupling 31
- scale-up reactor 38–42
- workup parameters reaction 35–37
- drug product 23
- drug substance 24
- good manufacturing practice 24
- impurity control
- ICH Q3D 50
- multi-step synthesis 49
- synthetic route
- cyclopropylhydrazine 26
- genotoxic impurities 26
- retrosynthetic approaches 26
- Ullmann coupling 27
- (acyl)M(carboxylate) 286
- additive manufacturing 270, 271
- aerobic oxidation 26, 30, 32–35, 37–38
- Agitated Thin Film Evaporator (ATFE) 131–132, 289
- air-stable catalysts 260
- aliskiren 121–132, 241, 249–252, 254
- alkene geometry 102, 107, 108, 110
- alkene stereochemistry 107–108
- cis*-alkenes 272, 274
- alkyl chloride 122, 125
- alkyl/acyl/alkenyl, heterocycles 185–187
- alkylation 9, 145, 162, 177, 185–187, 299
- (alkyl)M(carboxylate) intermediate 286
- aminations 42, 43, 45, 51–52, 204, 225–228
- ammonium chloride 247, 248
- ammonium pyrrolidinedithiocarbamate (APDTC) 46
- amphiphiles 203, 206, 209, 216, 221, 228, 229
- micelles 205, 207
- Anarsia lineatella* 266
- angiotensin(II) receptor antagonists (ARBs) 173
- biphenyl methyl 174
- C–H activation methodology 176
- olmesartanmedoxomil 177

- anhydride decarbonylation 286
 a-olefins 269
 area percent purity (AP) 137
 aromatic heterocycles 186
N-arylbenzamides 194
 aryl bromide
 DoE 155
 disodium salt 1 140
 ethyl ester 4 139
 potential hydrolyses 146
 TMAOAc 145
 aryl electrophile 96, 100, 102
 aryl lithium chemistry 80–81
 arylation, nitro compounds 228–229
 (+)-Aspewentin-B 299
 asymmetric hydrogenation 14–15,
 239, 241–242, 244, 246, 247–252,
 254
- b**
- batch process, time scale 62
 benzoic acids, C–H activation 221, 223
 benzoxazole 84–86
 biaryl compounds 172–173, 212
 biaryl/heterobiaryl synthesis
 green solvents 181
 organic solvents 172
k-bis(2 ethylhexyl)phosphate (BEHPK)
 178
 bisphosphines 100, 109, 241, 247
 “Boc-effect,” 274
 “N-Boc-effect,” 264
 borohydride reactions 253
 boronic acid toolbox 82
 borylation 5, 8, 10, 13, 82, 228
 British Compressed Gas Association
 247
 bromomethyltrifluoroborate 81–82
 Buchwald–Hartwig amination 23
 conditions 42
 NaTMT 46, 47
 Pd(*dba*)DPEPhos pre-catalyst 45–46
 scale-up and manufacturing 48
 screening condition formations
 43–45
 solubility studies 50
- c**
- C–H activation by C–C bond
 green solvents 181–185
 organic solvents 172–180
 C–H activation by C–O/N bond
 heterocycle synthesis 187–196
 organic solvents 187–189
 C–H bond activation 12–13, 173, 181,
 182
 C–H arylations 173, 177–180,
 183–185, 221, 223–225
 candesartan cilexetil synthesis
 173–175, 177, 196
 carbometalation 2, 3
 carbon monoxide (CO) 6, 8, 13, 14,
 186, 285–288, 296
 carbon–carbon bond formation 259
 carbon–hydrogen bond activation 2, 5,
 96
 carbonyl compounds 8, 9, 15, 16, 252,
 299–300
 carbonylation 6, 13
 catalyst loadings, minimization 239
in-situ catalyst system 241
 catalytic asymmetric hydrogenation
 241
 catalytic cycle 11, 161
 cyclization of 1 to 2 and formation
 161
 metathesis reactions 16
 catalytic hydrogenation 239, 252
 catalytic reactions 197, 210, 216, 225,
 245, 287–289, 300
 cationic rhodium complexes 246
 Chan–Lam coupling
 aerobic oxidation 32
 aerobic oxidation on scale 37
 Cu-catalyzed 29, 39
 defined 28
 homogenous conditions 31
 oxidative coupling 31
 scale-up reactor 38
 workup parameters reaction 35
 Chemistry Manufacturing and Controls
 (CMC)
 defined 23

- chemo-selective aldehyde
 - hydrogenation 252, 253
 - chemoselectivity 67
 - cholesteryl ester transfer protein (CETP) 179
 - cis*-catalyst 271
 - co-solvent technique 210
 - coatings 271
 - column chromatography 246
 - column purification 295
 - continuous flow technology
 - clogging flow chemistry 71
 - construction material 72
 - feedstock solution 69
 - low temperature hardware 69
 - safety concept, emergency strategies 73
 - start-up and shut-down operation 72
 - continuous stirred tank reactors (CSTRs) 29, 77, 79, 84
 - contract manufacturing organization (CMO) 23, 84
 - conventional batch synthesis 9
 - coupling reaction
 - model study 130
 - cross metathesis (CM) 261, 264–268
 - cross-coupling reactions 10
 - C–H bond activation 12–13
 - carbonylation 13
 - catalytic cycles 11
 - micellar catalysis 13–14
 - non-precious metals 91
 - cross-couplings
 - HandaPhos technology 215
 - iron ppm palladium technology 217
 - nano-nickel technology 214
 - cross-couplings in water
 - highly valuable reactions
 - aminations 225–228
 - arylation of nitro compounds 228–229
 - borylation 228
 - C–H arylations 221–225
 - heck coupling 217–219
 - Negishi couplings 219–221
 - pharmaceutical industry 229–234
 - Suzuki–Miyaura couplings 212–217
 - micellar catalysis
 - aqueous surfactant solution 206–207
 - efficiency 209–210
 - micellization 205, 206
 - nature of catalyst 208–209
 - order of addition 210–211
 - product precipitation/extraction 211
 - reaction temperature 207
 - size of micelles 207–208
 - trace metal 211, 212
 - crude reaction mixture 35–38, 243, 253
 - crystallization 35–37, 42, 43, 46–51, 53, 56–57, 109, 137, 145, 146, 150, 154, 158, 164, 177, 233, 264
 - drying 166–168
 - cyclometalation reaction 5
 - 1,5-cyclooctadiene (COD) 8
 - cyclooctadiene ligand, hydrogenation of 241
 - cyclopropylhydrazine 27
 - cycloruthenation 195
 - p*-cymene 173, 178, 181–183, 185–186, 191, 194–196, 241
- d**
- D-glucosamine, sodium
 - diethyldithiocarbamate (NaDETC) 46
 - de-hydro- β -amino acid 247
 - decarbonylation 6, 16, 283–300
 - of fatty acids 286
 - of two carboxylic acids 293
 - dehydrative decarbonylation 16, 285, 290, 296
 - catalytic mechanism 285, 286
 - ester decarbonylation 297–299
 - milder temperatures
 - PdCl₂/XantPhos/(tBu)₄biphenol system 291–293
 - well-defined Pd-bis(phosphine) precatalysts 294–295
 - nickel & iron catalysis 295–297

- dehydrative decarbonylation (*contd.*)
Rh-, Pd- & Ir-catalysis
 early studies 286–289
 reaction 291
 recent studies 289–291
sacrificial anhydride 285–286
synthetic utility, α -vinyl carbonyl
 compounds 299–300
- design of experiments (DoE) 7,
 154–156, 158
 aryl bromide 155
 cyclization reaction 155
 fractional factorial 156
 goal of 154
- 1,2-dibromoethane (DBE) 123–124,
 131
- dichloromethane (DCM) 46, 211, 273
- dicyclopentadiene (DCPD) 260, 262,
 268, 270
- diethyl carbonate (DEC) 182
- difluorobenzaldehyde 80
- difluorotoluene 80
- dihydrocinnamic acid 290
- 2,3-dihydrofurans 187
- dihydroisoquinolines 187, 193, 241
- 3,4-dihydro-isoquinolines 193
- dilution 71, 82, 262, 264, 273
- 2,4-dimethoxybenzyl (DMB) 177
- N,N*-dimethylacetamide (DMAc)
 process 141
 vs. DMF 149
 KOAc 141
 NaOH 149
 TMAOAc 143
 crystallization and drying 166
 cyclization reaction 152
 hydrolysis 164
 impurity formation 160
- N,N'*formati formation, 1605 (DMPU)
 291
- dimethyl sulfate (DMS) 80
- dimethylformamide (DMF) 31, 79, 80,
 102, 140–150, 168, 181, 188,
 217–218, 229, 273
 vs. DMAc cyclization reactions 149
 hydrolysis 149
- dimethylphenylphosphine (Me_2PhP)
 287–288
- 3,3'-disubstituted oxindoles 96, 97,
 113
- DPEPhos 43–46, 290–292, 294, 296,
 298
- drugs, synthesis of 262
- dynamic light scattering (DLS) 216
- e**
- (*E*)-5-decenol 266
- (*E*)-5-decenyl acetate 266
- edivoxetine 77, 79–80
- electrolyte-free water 205
- electron transfer reaction 6
- Elevance's alkenyolysis 273
- enantioselective synthesis
 alkene stereochemistry 107–108
 ligand screening 107
 mechanistic studies 110–113
 neutral vs. cationic pathways
 108–109
 nickel pre-catalyst complex synthesis
 109
 substrate scope exploration 110
- ester decarbonylation 297–299
- ethyl acetate (EtOAc) 46, 184, 211, 273
- ethylene (C_2) oligomerization 285
- ethylenediamine tetraacetate hydrate
 (NaEDTA) 46
- exogenous ligand 287
- exothermic reactions 76, 79, 86
- f**
- $\text{Fe}(\text{acac})_3$ 129
- flash chemistry 65
 chemoselectivity 67–68
 functional group tolerance 65–66
 selectivity 66–67
 stoichiometry 67–68
- fluorinated ethylene propylene (FEP)
 72–73
- focused beam reflectance measurement
 (FBRM) 49
- Fourier transform infra-red (FTIR) 49
- Fries*-rearrangement 68

g

genotoxic impurities (GTIs) 26
 GlaxoSmithKline (GSK) 81
 Good Manufacturing Practice (GMP)
 24, 54, 57
 Grela catalyst 261, 263
 Grignard reagents 9, 64, 75
 0–5°C stability 125
 alkyl chloride 125
 THF 124, 125, 127
 Grignard, Victor 8–10, 14
 Grubbs' catalyst 265, 271

h

halide anions 246, 247
 halogen-dance 67
 Heck-type reactions 217
 hepatitis C virus (HCV) 262
 NS5B inhibitor 137, 138
 heptadecenes 296
N-heterocycles 193
 heterocycle synthesis 187–196
 organic solvents 187–189
N-heterocyclic carbene ligand 298
 hex-5-en-1-yl acetate 266
 high performance liquid
 chromatography (HPLC)
 32–34, 41–46, 48–49, 53, 107,
 130, 137, 154, 158, 160
 high vacuum distillation (HVD) 131,
 141
 highly toxic raw materials (HCN) 283
 highly valuable reactions, water
 aminations 225–228
 arylation of nitro compounds
 228–229
 borylation 228
 C–H arylations 221–225
 Heck coupling 217–219
 Negishi couplings 219–221
 pharmaceutical industry 229–234
 Suzuki–Miyaura couplings 212–217
 homogeneous catalyst 18, 171, 239,
 250, 252
 homogeneous hydrogenation 239, 240
 additive effects 247–249
 aliskiren approach 249–252

catalyst selection, screening
 approaches 240–244
 chemo-selective aldehyde
 hydrogenation 252–253
 reaction considerations 244–247
 Hoveyda–Grubbs ruthenium catalysts
 261, 263, 273
 β -hydride elimination 2, 4, 12, 221,
 286, 300
 hydrofluoric acid (HF) 81
 β -hydrogen elimination 3–4, 11, 127,
 128
 hydrogen gas 240, 244, 245, 247
 hydrogen pressure 241, 243–245, 249
 “hydrogen-starvation” conditions 245
 hydrogenated metathesized soybean oil
 (HMSBO) 265
 hydrogenation feedstock 247
 hydrogenation reactions 3, 8, 14–15,
 241, 244–246, 250, 253, 254
 hydrogenation reactor 245, 252
 hydrometalation 2–4
N-hydroxysuccinimide sodium salt
 187–188

i

impurity control
 ICH Q3D 50
 multi-step synthesis 49
 inadequate stirring, of hydrogenation
 reaction 245
 indoles 109, 137, 145, 162, 185,
 192–193, 223
in-situ generated catalysts 241
 International Conference on
 Harmonisation (ICH) guidelines
 23–24, 48–50, 122
 iridium catalyst 239
 iridium-bisphosphine catalysts 241
 iron catalyzed Kumada–Corriu coupling
 12, 121–135

j
 Josiphos ligand 247

k
 KOAc/DMAc process 141
 Kumada coupling 12, 94

- Kumada cross-coupling reaction 12, 121–135
- Kumada–Corriu coupling
 active pharmaceutical ingredient 122
 Aliskiren 122
 alkyl chloride 125
 ATFE 131–132
 DBE equivalents 123–124
 Grignard reagent solvent 124–125
 Grignard stirring time 125
 iron catalyzed 127–128
 Mg equivalence 123
 NMP equivalents 129
 pilot scale 129–131
 substrate 4 equivalents 129
 THF 124, 125
 types 121
- I**
- L-ligands 271, 274
- Li and Mg processes, flow mode
 batch operation 62–64
 flash chemistry
 chemoselectivity 67–68
 functional group tolerance 65–66
 selectivity 66–67
 stoichiometry 67–68
 metalated species 62
 temperature profiles 64–65
- ligand screening 43, 98–100, 101, 107, 137
- lignocellulosic biomass 283
- liquid and/or gas chromatography 242, 243
- m**
- Mannich-type reaction 77, 78
- mass spectrometry 216, 243
- MeMgCl 130–131
- mercaptinicotinic acid (MNA) 263, 264, 276
- metal catalyzed cross-coupling reactions 2, 12, 24, 91, 121
- metal-catalyzed carbonylation 13
- metalation reactions 66
- metal–organic compounds 1–7
- metathesis polymerization 2, 259, 261, 268
- metathesis reactions 15–16, 261, 268, 270, 273
- methacrylic acid (MAA) 283
- methyl *tert*-butyl ether (MTBE) 143, 150, 152, 164–167
- methyl vinyl ketone (MVK) 285
- methylaluminoxane (MAO) activator 17
- methylene boronate synthesis 81
- methylidene 268
- Mg equivalence 123
- micellar catalysis 13, 203
 advantages of 211
 aqueous surfactant solution 206–207
 cinnamate esters 224
 co-solvent technique 210
 efficiency 209–210
 micellization 205, 206
 nature of catalyst 208–209
 novartis pharmaceuticals 231
 order of addition 210–211
 product precipitation/extraction 211
 reaction temperature 207
 size of micelles 207–208
 trace metal 211, 212
- Micellar Heck couplings 219
- Micelle-assisted Negishi couplings 220
- Micelles-enabled couplings
 (iso)quinoline systems 216, 218
- micellization 205, 206
 higher temperature 207
- migratory insertion reactions 2, 6, 105, 110, 195
- milder temperatures
 PdCl₂/XantPhos/(*t*Bu)₄biphenol system 291–294
 well-defined Pd-bis(phosphine) precatalysts 294–295
- “mixed anhydride,” 286, 300
- Mizoroki–Heck coupling
 oxindoles synthesis 96
 palladium 92

- palladium-catalyzed intramolecular
96
- Mizoroki–Heck reaction 12
- myristic acid 31–33, 35–36, 288, 289
- n**
- N*-Boc functional group 264
- N*-heterocyclic carbene (NHC) 45,
261, 271–272, 298
- NaOH 43, 146–150, 152, 226, 289, 294
DMAc 149
- Negishi couplings 94, 219–221
- neomenthylidiphenylphosphine (NMDP)
92
- neutral vs. cationic pathways 108
- N*-heterocyclic carbene (NHC) 45,
261, 271–272, 298
- Ni-catalyzed decarbonylation reactions
296
- Ni-catalyzed intramolecular
Mizoroki–Heck coupling
catalytic cycle 107
non-precious metal catalysts 91
- nickel pre-catalyst complex synthesis
109
- nickel-catalysis
advantages of 94
- nickel-catalyzed classical couplings 95
- nickel-catalyzed Mizoroki–Heck
couplings
catalytic cycle 99
cyclization, scope of 103
enantioselective 94, 95
enantioselective synthesis
alkene stereochemistry 107–108
ligand screening 107
mechanistic studies 110, 112, 113
neutral vs. cationic pathways
108–109
nickel pre-catalyst complex
synthesis 109
substrate scope exploration 110,
111
palladium-catalyzed system 93
quaternary stereogenic centers,
oxindoles
aryl electrophile 100
ligand screening 98, 100
methodology limitations 104
precedents 97
reaction mechanism 104, 105
reducing agent 97–98
robustness screening test 102
reaction condition types 93, 94
reaction mechanism 105
- N*-methylpyrrolidine (NMP) 29, 31,
127–129, 140–141, 143, 149, 173,
177–182, 184–185, 189, 191,
228–229, 264, 294, 299
- p*-nitrophenol esters 297–298
- nonionic amphiphiles 205–206, 228,
229
- non-precious-metal-catalysis 97, 113
advantage 91–92
- non-ruthenium catalysts 260, 261
Norsorex[®] 268
NS5B inhibitor 137, 138
- nucleophilic abstraction 2, 6
- o**
- olefin formation reactions
dehydrative decarbonylation 16
metathesis reactions 15–16
photoredox catalysis for organic
synthesis 17
poly- or oligomerisation processes
17
starting materials 16–17
Wittig reaction 15
- olefin metathesis 16
industrial uses
CM 264–268, 269
RCM 262–264
ROMP 268, 270
- non-ruthenium catalysts 260, 261
- reaction considerations 270
application guide and availability
274
catalyst choice 271–273
catalyst loading 273
overall handling 274
reaction concentration 273–274
solvent 273
- ruthenium catalysts 261–262

- olefin metathesis (*contd.*)
 - troubleshooting
 - catalyst
 - decomposition – isomerization 277
 - catalyst removal 275–276
 - functional group tolerance 276
 - substrate purity 276–277
 - α -olefins 296
 - oligomerisation processes 17
 - organic synthesis 1–18, 54, 61–62, 121, 133–134, 185, 204, 205, 259
 - photoredox catalysis 17
 - organomagnesium species 64
 - organometallic chemistry
 - continuous flow technology
 - clogging flow chemistry 71–72
 - construction material 72–73
 - low temperature hardware 69
 - safety concept, emergency strategies 73
 - start-up and shut-down operation 72
 - flow process, development 73
 - aryl lithium chemistry 80–81
 - benzoxazole 84–86
 - bromomethyltrifluoroborates 81–82
 - edivoxetine manufacture 77, 79–80
 - feasibility study 74–75
 - technical feasibility 75–76
 - Verubecestat (MK-8931) 77, 78
 - Li and Mg processes, flow mode
 - batch operation 62
 - metalated species 62–64
 - temperature profiles 64–65
 - organometallic complexes 1, 2, 4, 6–7, 10, 17, 240–241
 - organometallic compounds
 - cross-coupling reaction 10
 - C–H bond activation 12–13
 - carbonylation 13
 - micellar catalysis 13–14
 - defined 1
 - electronic applications 1
 - hydrogenation reactions 14–15
 - industrial process 7
 - olefin formation reactions
 - dehydratedecarbonylation 16
 - metathesis reactions 15–16
 - photoredox catalysis for organic synthesis 17
 - poly- or oligomerisation processes 17
 - starting materials 16–17
 - Wittig reaction 15
 - organic synthesis 2–7
 - polymer applications 2
 - stoichiometric organometallic reagents
 - conventional batch synthesis 9–10
 - industrial-scale organic synthesis 10
 - organometallic reactions 64
 - carbometalation 3
 - carbon-hydrogen bond activation 5
 - cyclometalation 5
 - electron transfer 6
 - β -hydrogen elimination 3
 - hydrometalation 3
 - migratory insertion 6
 - nucleophilic abstraction 6
 - organometallic substitution reactions 4
 - oxidative addition 2
 - reductive elimination 2
 - types 2
 - organometallic reactivity 6, 17
 - organometallic reagents 3, 9, 10, 12, 13, 64, 66, 72, 74, 75, 77, 121, 172
 - organometallic substitution reactions 2, 4–5
 - Ortho*-lithiated aryl benzyl ethers 67
 - oxidative addition 2–3, 5, 10, 12, 105, 110, 114, 161, 191, 214, 216, 286, 300
 - oxidative coupling 30, 35
 - δ -oxocarboxylic acids 299

p

 - palladium
 - Mizoroki–Heck coupling 92

- palladium catalysts 12, 91–93, 96, 150, 152, 216, 223, 233, 288, 289, 294
 palladium catalyzed reaction 291
 palladium precursors 292, 294
 palladium(II) acetate (Pd(OAc)₂) 137
 palladium-catalyzed cross-couplings 11, 13, 203, 208, 212
 palladium-catalyzed cyclization of 1 140
 palladium-catalyzed intramolecular direct arylation
 aryl bromide ethyl ester 4 139
 KOAc/DMAc process 141–143
 TMAOAc/DMAc process 143
 crystallization and drying 166
 cyclization reaction 152
 hydrolysis 164
 impurity formation 160
 palladium-catalyzed protocol 291
 Pd(bis-phosphine) precatalysts 294
 Pd(dba)DPEPhos pre-catalyst 45–46
 Pd-bis(phosphine) complexes 294
 peach twig borer 265–266
 peroxide value (PV) 276
 pharmaceutical industry 10, 13, 16, 26, 56, 61, 86, 134, 181, 204, 212, 229–234, 259, 262
 phosphine ligands 139, 175, 179, 181–183, 187, 240, 268, 287–288, 290, 292, 294, 296–297
 photocatalytic Pschorr reaction 6, 7
 photoredox catalysis 235
 organic synthesis 17
 pipes-in-series reactor
 design 32, 33
 reaction kinetics 40
 vapor-liquid 33
 vertical size 39
 pivalate (KOPiv) 93, 182
 pivalic anhydride 289–291
 platinum group metals (PGMs) 7–8
 plug flow reactors (PFRs) 33, 77, 79
p-methoxybenzoyl (PMB) 177
 polar solvents 273, 291, 294
 polymerisation processes 9, 17, 270
 polyethylene glycol (PEG) 181, 193, 208, 211
 polyfluoroalkoxy (PFA) 72–73, 82, 84
 polymers 1, 16, 17, 70, 72, 259, 268, 270, 271, 278, 290, 300
 organometallic compounds 2
 polyoxyethanyl α -tocopheryl sebacate (PTS)
 allylic ethers coupling 213
 Suzuki–Miyaura couplings 212
 polysiloxanes 2
 polytetrafluoroethylene (PTFE) 72, 74, 82, 84
 popular ruthenium catalysts 261
 potassium acetate (KOAc) 141–143, 145, 150, 168, 178, 182, 228
 pre-catalyst Pd(dba)DPEPhos 45
 pre-formed catalysts 45, 241
 process analytical technology (PAT) 49, 69, 76, 82, 85
 process-hazard-analysis (PHA) 73
 purification technique 49, 239
- q**
- quality by design (QbD) 49
 quaternary stereogenic centers, oxindoles
 alkene moiety 100
 aryl electrophile 100, 102
 ligand screening 98, 100, 101
 methodology limitations 104
 precedents 97, 100
 reaction mechanism 104–105
 reducing agent 97–98
 robustness screening test 102
- r**
- rate-determining step (RDS) 294
 reaction injection molding (RIM) 268
 reaction kinetics
 pipes-in-series reactor 34
 temperature effect on conversion 35
 recrystallization 204, 230, 239, 275
 reductive elimination 2–3, 10, 162, 179, 191, 193, 195, 216, 286, 300
 Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) 31, 143, 149

- relative area percent (RAP) 154, 158, 164
- rhodium catalyzed decarbonylation 287
- [Rh-(S)-Phanephos(cod)]BF₄ 252
- ring closing metathesis (RCM) 259, 261–264
- ring opening metathesis polymerization (ROMP) 2, 259, 268–271
- robustness screening test 102
- Rolapitant 262
- ruthenium (II) complexes 171, 173, 181–182, 186, 193–194
- ruthenium catalyzed
- alkyl/acyl/alkenyl substitution on heterocycles 185–187
 - C–H activation by C–C bond
 - green solvents 181–185
 - organic solvents 172–182
 - C–H activation by C–O/N bond
 - organic solvents 187–189
- ruthenium catalyst chelator 263
- ruthenium catalysts 14, 175, 178, 185, 187, 189, 191, 196, 260–263, 266, 271–277
- ruthenium methylenide 268
- ruthenium-based catalysts 196, 260
- S**
- sacrificial anhydride (Ac₂O) 285, 286
- cis*-selective catalyst 273, 274
- α -selectivity 288, 292–299
- Shell Higher Olefin Process (SHOP) 3, 4
- SiliabondThiol (Si-Thiol) 46, 47, 53
- silicone 2
- sodium borohydride 176, 252, 253
- sodium formate 146–149, 182, 185
- sodium phenoxide (NaOPh) 42–43
- Sonogashira couplings 209
- in water 216
- steady state profile
- for manufacturing scale 42
 - for reactions 41
- stearic acid 286–289, 291, 293–296
- stereodetermining oxidative 113
- stereoselection mechanism 113
- stirred tank (SS) reactor 29, 70, 131
- stoichiometric organometallic reagents
- conventional batch synthesis 9
 - industrial-scale organic synthesis 10
- stoichiometry 32, 36, 41, 64, 67–70, 72, 74–75
- substrate purity 246, 262, 276–277
- suitable solvents 182, 240
- Suzuki couplings reaction 12
- Suzuki–Miyaura couplings 11, 12, 81, 94, 212
- copper and ppm levels 215
 - organic solvent stage 213
 - PTS 212
- t**
- TamoxifenTM 3
- tetrabutylammonium acetate (TBAOAc) 141
- tetrahydrofuran (THF) 31, 33, 35–38, 72, 74, 79, 81, 82, 84, 124–125, 127, 130–132, 209, 220, 264
- large scale batches 131
- tetramethylammonium acetate (TMAOAc) 141, 143–168
- aryl bromide 145
- tetramethylethylenediamine (TMEDA) 219–221
- thiol-Grubbs–Hoveyda catalysts 271
- cis*-thiol Grubbs–Hoveyda catalysts 271
- TMAOAc/DMAc process 143
- commercial process 152
 - crystallization and drying 166–168
 - cyclization process parameters 157, 159
 - cyclization reaction 152–164
 - hydrolysis 164–165
 - impurity formation 160–164
 - palladium loading study 160
 - Pd Loading at Pilot Scale 160
- transition metal catalysts 171–172, 300
- transition-metal dehydrative decarbonylation 286

- transtaganolide C 299
- 1,3,5-Triazine-2,4,6-trithiol trisodium salt (NaTMT) 46–47
- 2, 4, 6-trimethylbenzenesulfonate (TMBSK) 177–178
- trimethylsilyl bromide (TMSBr) 176
- triphenylphosphine (PPh₃) 175, 178, 179, 189, 287, 289–290, 292, 294, 297–298
- triruthenium dodecacarbonyl 191
- tungsten catalysts 261
- turn over frequencies (TOF) 2, 7, 239, 247
- turn over number (TON) 2, 7, 228, 239, 246, 266–268, 273, 276, 288–289, 293–294
- u**
- Ullmann coupling 27–28
- v**
- Vaska's complex 3–5, 290
- Verubecestat (MK-8931) 77
- α -vinyl carbonyl compounds 299–300
- w**
- Weinreb's amides 195
- Wilkinson's catalyst 6, 287
- Wittig olefination 15
- Wittig reaction 15
- Wittig, Georg 9, 15
- workup parameters reaction 35–37
- Wurtz-coupling 75
- x**
- XantPhos 43, 45, 290–294, 298–300
- z**
- Ziegler–Natta (ZN) polymerisation process 2, 6, 17

