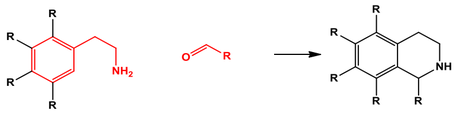
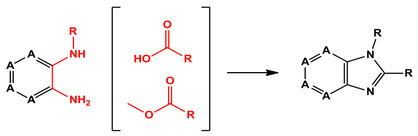
1



{Pictet-Spengler}
[cH1:1]1:[c:2](-[CH2:7]-[CH2:8]-[NH2:9]):[c:3]:[c:4]:[c:5]:[c:6]:1.[#6:11]-[CH1;R0:10]=[OD1]>>[c:1]12:[c:2](-[CH2:7]-[CH2:8]-[NH1:9]-[C:10]-2(-[#6:11])):[c:3]:[c:4]:[c:5]:[c:6]:1
c1cc(CCN)ccc1 CC(=O)

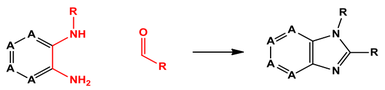
Step potentially produces regiosiomers because of symmetric substructure definition.

2



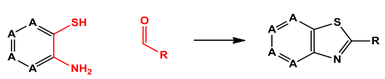
{benzimidazole_derivatives_carboxylic-acid/ester}
[c;r6:1](-[NH1;$(N-[#6]):2]):[c;r6:3](-[NH2:4]).[#6:6]-[C;R0:5](=[OD1])-[#8;H1,$(O-[CH3])]>>[c:3]2:[c:1]:[n:2]:[c:5](-[#6:6]):[n:4]@2
c1c(NC)c(N)ccc1 CC(=O)O
Any sixmembered aromatic heterocycle

3



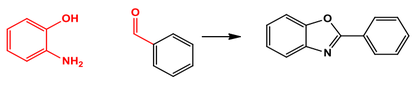
{benzimidazole_derivatives_aldehyde}
[c;r6:1](-[NH1;$(N-[#6]):2]):[c;r6:3](-[NH2:4]).[#6:6]-[CH1;R0:5](=[OD1])>>[c:3]2:[c:1]:[n:2]:[c:5](-[#6:6]):[n:4]@2
c1c(NC)c(N)ccc1 CC(=O)
Any sixmembered aromatic heterocycle

4



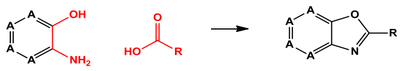
{benzothiazole}
[c;r6:1](-[SH1:2]):[c;r6:3](-[NH2:4]).[#6:6]-[CH1;R0:5](=[OD1])>>[c:3]2:[c:1]:[s:2]:[c:5](-[#6:6]):[n:4]@2
c1c(S)c(N)ccc1 CC(=O)
Any sixmembered aromatic heterocycle

5



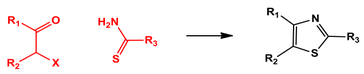
{benzoxazole_arom-aldehyde}
[c:1](-[OH1;$(Oc1ccccc1):2]):[c;r6:3](-[NH2:4]).[c:6]-[CH1;R0:5](=[OD1])>>[c:3]2:[c:1]:[o:2]:[c:5](-[c:6]):[n:4]@2
c1cc(O)c(N)cc1 c1ccccc1C(=O)

6



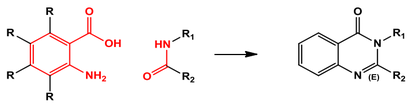
{benzoxazole_carboxylic-acid}
[c;r6:1](-[OH1:2]):[c;r6:3](-[NH2:4]).[#6:6]-[C;R0:5](=[OD1])-[OH1]>>[c:3]2:[c:1]:[o:2]:[c:5](-[#6:6]):[n:4]@2
c1cc(O)c(N)cc1 CC(=O)O
Any sixmembered aromatic heterocycle

7



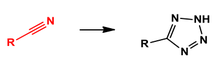
{thiazole}
[#6:6]-[C;R0:1](=[OD1])-[CH1;R0:5](-[#6:7])-[*;#17,#35,#53].[NH2:2]-[C:3]=[SD1:4]>>[c:1]2(-[#6:6]):[n:2]:[c:3]:[s:4][c:5]([#6:7]):2
CC(=O)C(I)C NC(=S)C
X=Cl, Br, I

8



{Niementowski_quinazoline}
[c:1](-[C;$(C-c1ccccc1):2](=[OD1:3])-[OH1]):[c:4](-[NH2:5]).[N;!H0;!$(N-N);!$(N-C=N);!$(N(-C=O)-C=O):6]-[C;H1,$(C-[#6]):7]=[OD1]>>[c:4]2:[c:1]-[C:2](=[O:3])-[N:6]-[C:7]=[N:5]-2
c1c(C(=O)O)c(N)ccc1 C(=O)N

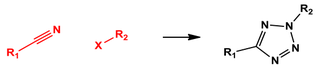
9



{tetrazole_terminal}
[CH0;$(C-[#6]):1]#[NH0:2]>>[C:1]1=[N:2]-N-N=N-1
CC#N

Transform with NaN3

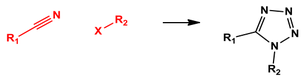
10



{tetrazole_connect_regioisomere_1}
[CH0;$(C-[#6]):1]#[NH0:2].[C;A;!$(C=O):3]-[*;#17,#35,#53]>>[C:1]1=[N:2]-N(-[C:3])-N=N-1
CC#N CBr

Not regioselective; alternative product is CC1=NN=N-N1(C)
Additional step: substitute halogen with azide (NaN3)

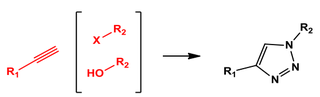
11



{tetrazole_connect_regioisomere_2}
[CH0;$(C-[#6]):1]#[NH0:2].[C;A;!$(C=O):3]-[*;#17,#35,#53]>>[C:1]1=[N:2]-N=N-N-1(-[C:3])
CC#N CBr

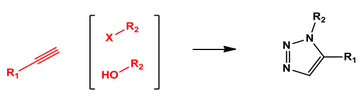
Not regioselective; alternative product is CC1=NN(C)N=N1
Additional step: substitute halogen with azide (NaN3)

12



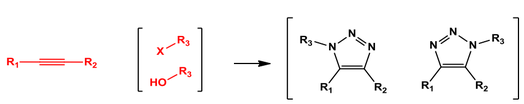
{Huisgen_Cu-catalyzed_1,4-subst}
[CH0;$(C-[#6]):1]#[CH1:2].[C;H1,H2;A;!$(C=O):3]-[*;#17,#35,#53,OH1]>>[C:1]1=[C:2]-N(-[C:3])-N=N-1
CC#C CCBr
X=Cl,Br,I; R1:aryl, alkyl; R2: aliphatic carbon
alcohols can be directly converted to azides under Mitsunobu conditions
see March p.1612; Chengzhi,Org. Lett., 2000, 2 (13), pp 1959–1961; Thompson, J. Org. Chem., 1993, 58 (22), pp 5886–5888
Additional step: substitution of halogen or hydroxy group (Mitsunobu conditions) with azide (NaN3). Stereochemistry at secondary halides/alcohols needs to be considered.

13



{Huisgen_Ru-catalyzed_1,5_subst}
[CH0;$(C-[#6]):1]#[CH1:2].[C;H1,H2;A;!$(C=O):3]-[*;#17,#35,#53,OH1]>>[C:1]1=[C:2]-N=NN(-[C:3])-1
CC#C CCBr
X=Cl,Br,I; R1:aryl, alkyl; R2: aliphatic carbon
Ruthenium catalysis instead of copper gives 1,5-substituted triazoles; Alcohols can be directly converted to azides under Mitsunobu conditions
see March p.1612; Chengzhi,Org. Lett., 2000, 2 (13), pp 1959–1961; Thompson, J. Org. Chem., 1993, 58 (22), pp 5886–5888
Additional step: substitution of halogen or hydroxy group (Mitsunobu conditions) with azide (NaN3). Stereochemistry at secondary halides/alcohols needs to be considered.

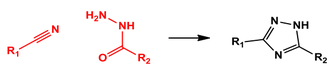
14



{Huisgen_disubst-alkyne}
[CH0;$(C-[#6]):1]#[CH0;$(C-[#6]):2].[C;H1,H2;A;!$(C=O):3]-[*;#17,#35,#53,OH1]>>[C:1]1=[C:2]-N=NN(-[C:3])-1
CC#CC CCBr
X=Cl,Br,I; R1:aryl, alkyl; R2: aliphatic carbon

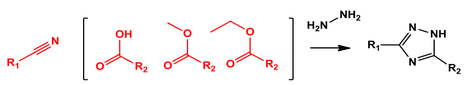
Not regioselective: in case the alkyne is non-symmetrically substituted both regioisomers are likely to be formed.
Additional step: substitution of halogen or hydroxy group (Mitsunobu conditions) with azide (NaN3). Stereochemistry at secondary halides/alcohols needs to be considered.

15



{1,2,4-triazole_acetohydrazide}
[CH0;$(C-[#6]):1]#[NH0:2].[NH2:3]-[NH1:4]-[CH0;$(C-[#6]);R0:5]=[OD1]>>[N:2]1-[C:1]=[N:3]-[N:4]-[C:5]=1
CC#N NNC(=O)C

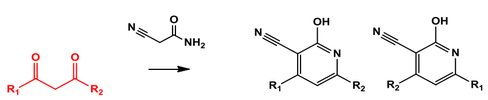
16



{1,2,4-triazole_carboxylic-acid/ester}
[CH0;$(C-[#6]):1]#[NH0:2].[CH0;$(C-[#6]);R0:5](=[OD1])-[#8;H1,$(O-[CH3]),$(O-[CH2]-[CH3])]>>[N:2]1-[C:1]=N-N-[C:5]=1
CC#N OC(=O)C

Additional step: nuc. sub. with hydrazine

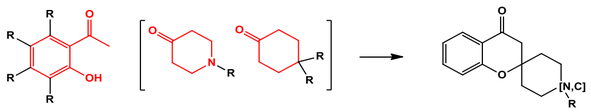
17



{3-nitrile-pyridine}
[#6;!$([#6](-C=O)-C=O):4]-[CH0:1](=[OD1])-[C;H1&!$(C-[*;!#6])&!$(C-C(=O)O),H2:2]-[CH0;R0:3](=[OD1])-[#6;!$([#6](-C=O)-C=O):5]>>[c:1]1(-[#6:4]):[c:2]:[c:3](-[#6:5]):n:c(-O):c(-C#N):1
CC(=O)CC(=O)C
central C must at least have one H; substituent must not be anything else but C, but not a carboxylic acid; only one of carbonyles is allowed to be part of a ring
R1,R2 has to be C (aromatic, aliphatic), but not C=O

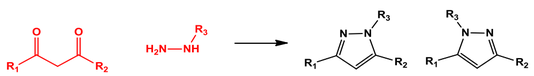
Step potentially produces regiosiomers because of symmetric substructure definition.

18



{spiro-chromanone}
[c:1](-[C;$(C-c1ccccc1):2](=[OD1:3])-[CH3:4]):[c:5](-[OH1:6]).[C;$(C1-[CH2]-[CH2]-[N,C]-[CH2]-[CH2]-1):7](=[OD1])>>[O:6]1-[c:5]:[c:1]-[C:2](=[OD1:3])-[C:4]-[C:7]-1
c1cc(C(=O)C)c(O)cc1 C1(=O)CCNCC1

19



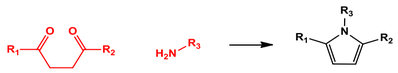
{pyrazole}
[#6;!$([#6](-C=O)-C=O):4]-[CH0:1](=[OD1])-[C;H1&!$(C-[*;!#6])&!$(C-C(=O)O),H2:2]-[CH0;R0:3](=[OD1])-[#6;!$([#6](-C=O)-C=O):5].[NH2:6]-[N;!H0;$(N-[#6]),H2:7]>>[C:1]1(-[#6:4])-[C:2]=[C:3](-[#6:5])-[N:7]-[N:6]=1
CC(=O)CC(=O)C NNC
central C must at least have one H, substituent must not be anything else but C, bu not a carboxylic acid; only one of carbonyles is allowed to be part of a ring
R1,R2 need to be C (aromatic, aliphatic), but not C=O; R3: H, C, even C=O possible

Step potentially produces regiosiomers because of symmetric substructure definition.

20

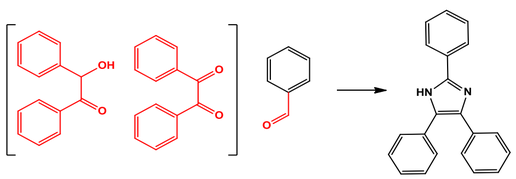
{phthalazinone}
[c;r6:1](-[C;$(C=O):6]-[OH1]):[c;r6:2]-[C;H1,$(C-C):3]=[OD1].[NH2:4]-[NH1;$(N-[#6]);!$(NC=[O,S,N]):5]>>[c:1]1:[c:2]-[C:3]=[N:4]-[N:5]-[C:6]-1
c1cc(C(=O)O)c(C(=O)C)cc1 NNC
any 6-membered aromatic heterocycle, also substituted
R2 must be carbon, but not C=O,C=S,C=N

21



{Paal-Knorr pyrrole}
[#6:5]-[C;R0:1](=[OD1])-[C;H1,H2:2]-[C;H1,H2:3]-[C:4](=[OD1])-[#6:6].[NH2;$(N-[C,N]);!$(NC=[O,S,N]);!$(N([#6])[#6]);!$(N~N~N):7]>>[C:1]1(-[#6:5])=[C:2]-[C:3]=[C:4](-[#6:6])-[N:7]-1
CC(=O)CCC(=O)C NC
the two central carbon in educt 1 can be substituted, but must have at least one H
edcut 2 has to be primary amine, also an N of hydrazine

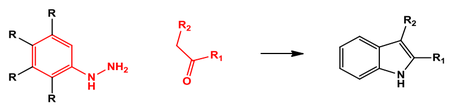
22



{triaryl-imidazole}
[C;$(C-c1ccccc1):1](=[OD1])-[C;D3;$(C-c1ccccc1):2]~[O;D1,H1].[CH1;$(C-c):3]=[OD1]>>[C:1]1-N=[C:3]-[NH1]-[C:2]=1
c1ccccc1C(=O)C(=O)c1ccc c1ccccc1C(=O)
educt 1: can be keto or hydroxy
educt 2: aldehyde connected to any aromatic system

Additional reactant: ammonium acetat

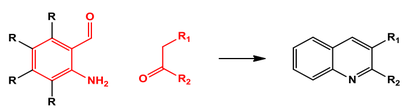
23



{Fischer indole}
[NH1;$(N-c1ccccc1):1](-[NH2])-[c:5]:[cH1:4].[C;$(C([#6])[#6]):2](=[OD1])-[CH2;$(C([#6])[#6]);!$(C(C=O)C=O):3]>>[C:5]1-[N:1]-[C:2]=[C:3]-[C:4]:1
c1ccccc1NN CCC(=O)C

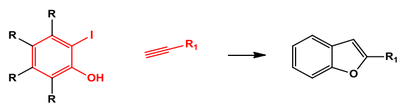
Step potentially produces regiosiomers because of symmetric substructure definition.

24



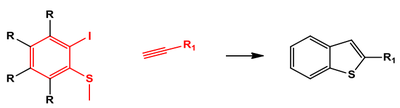
{Friedlaender chinoline}
[NH2;$(N-c1ccccc1):1]-[c:2]:[c:3]-[CH1:4]=[OD1].[C;$(C([#6])[#6]):6](=[OD1])-[CH2;$(C([#6])[#6]);!$(C(C=O)C=O):5]>>[N:1]1-[c:2]:[c:3]-[C:4]=[C:5]-[C:6]:1
c1cccc(C=O)c1N CCC(=O)C

25



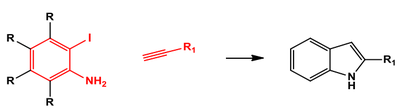
{benzofuran}
[*;Br,I;$(*c1ccccc1)]-[c:1]:[c:2]-[OH1:3].[CH1:5]#[C;$(C-[#6]):4]>>[c:1]1:[c:2]-[O:3]-[C:4]=[C:5]-1
c1cc(I)c(O)cc1 CC#C
bromide and iodide allowed

26



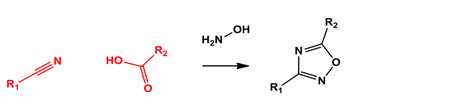
{benzothiophene}
[*;Br,I;$(*c1ccccc1)]-[c:1]:[c:2]-[SD2:3]-[CH3].[CH1:5]#[C;$(C-[#6]):4]>>[c:1]1:[c:2]-[S:3]-[C:4]=[C:5]-1
c1cc(I)c(SC)cc1 CC#C
bromide and iodide allowed

27



{indole}
[*;Br,I;$(*c1ccccc1)]-[c:1]:[c:2]-[NH2:3].[CH1:5]#[C;$(C-[#6]):4]>>[c:1]1:[c:2]-[N:3]-[C:4]=[C:5]-1
c1cc(I)c(N)cc1 CC#C
bromide and iodide allowed

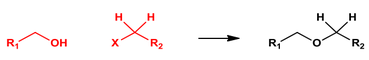
28



{oxadiazole}
[#6:6][C:5]#[#7;D1:4].[#6:1][C:2](=[OD1:3])[OH1]>>[#6:6][c:5]1[n:4][o:3][c:2]([#6:1])n1
CC#N CC(=O)O

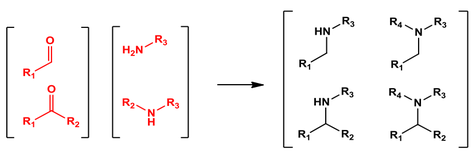
Additional step: convert nitrile to amidoxime by hydroxylamine

29



{Williamson ether}
[#6;$([#6]~[#6]);!$([#6]=O):2][#8;H1:3].[Cl,Br,I][#6;H2;$([#6]~[#6]):4]>>[CH2:4][O:3][#6:2]
CCO CCBr
primary halide (Cl, Br, I), hydroxy group may be attached to arom. system as well as aliphatic (prim, sec. or tert. carbon)

30



{reductive amination}
[#6:4]-[C;H1,$([CH0](-[#6])[#6]):1]=[OD1].[N;H2,$([NH1;D2](C)C);!$(N-[#6]=[*]):3]-[C:5]>>[#6:4][C:1]-[N:3]-[C:5]
CC(=O) NC

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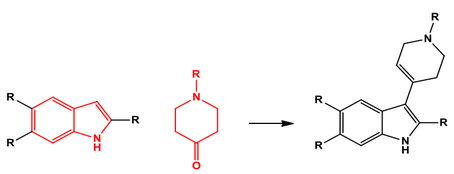
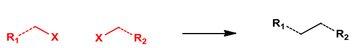
{Suzuki}
[#6;H0;D3;$([#6](~[#6])~[#6]):1]B(O)O.[#6;H0;D3;$([#6](~[#6])~[#6]):2][Cl,Br,I]>>[#6:2][#6:1]
c1ccccc1B(O)O c1ccccc1Br
any borinic acid (incl. cyclic)
X=Cl, Br, I

32



{piperidine_indole}
[c;H1:3]1:[c:4]:[c:5]:[c;H1:6]:[c:7]2:[nH:8]:[c:9]:[c;H1:1]:[c:2]:1:2.O=[C:10]1[#6;H2:11][#6;H2:12][N:13][#6;H2:14][#6;H2:15]1>>[#6;H2:12]3[#6;H1:11]=[C:10]([c:1]1:[c:9]:[n:8]:[c:7]2:[c:6]:[c:5]:[c:4]:[c:3]:[c:2]:1:2)[#6;H2:15][#6;H2:14][N:13]3
c1cccc2c1C=CN2 C1CC(=O)CCN1

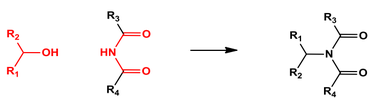
33



{Negishi}
[#6;$([#6]~[#6]);!$([#6]~[S,N,O,P]):1][Cl,Br,I].[Cl,Br,I][#6;$([#6]~[#6]);!$([#6]~[S,N,O,P]):2]>>[#6:2][#6:1]
CCBr CCBr

Additional step: formation of Zn halide

34



{Mitsunobu_imide}
[C;H1&$(C([#6])[#6]),H2&$(C[#6]):1][OH1].[NH1;$(N(C=O)C=O):2]>>[C:1][N:2]
CC(O)C CC(=O)NC(=O)C
R2: H, C

Inversion of stereo chemistry at chiral centers

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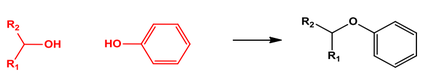
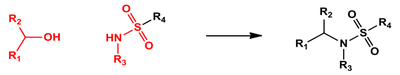


{Mitsunobu_phenole}
[C;H1&$(C([#6])[#6]),H2&$(C[#6]):1][OH1].[OH1;$(Oc1ccccc1):2]>>[C:1][O:2]
CC(O)C c1ccccc1O
R2: H, C

Inversion of stereo chemistry at chiral centers

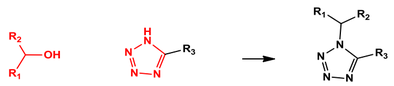
36



{Mitsunobu_sulfonamide}
[C;H1&$(C([#6])[#6]),H2&$(C[#6]):1][OH1].[NH1;$(N([#6])S(=O)=O):2]>>[C:1][N:2]
CC(O)C CNS(=O)(=O)C
R2: H, C

Inversion of stereo chemistry at chiral centers

37



{Mitsunobu_tetrazole_1}
[C;H1&$(C([#6])[#6]),H2&$(C[#6]):1][OH1].[#7H1:2]1~[#7:3]~[#7:4]~[#7:5]~[#6:6]~1>>[C:1][#7:2]1:[#7:3]:[#7:4]:[#7:5]:[#6:6]:1
CC(O)C N1=NNC=N1
R2: H, C

Not regioselective: alternative product is substituated at the N at position 2 instead of 1
Inversion of stereo chemistry at chiral centers

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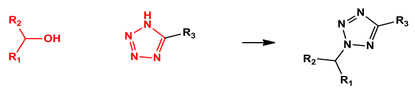

{Mitsunobu_tetrazole_2}
[C;H1&$(C([#6])[#6]),H2&$(C[#6]):1][OH1].[#7H1:2]1~[#7:3]~[#7:4]~[#7:5]~[#6:6]~1>>[#7H0:2]1:[#7:3]:[#7H0:4]([C:1]):[#7:5]:[#6:6]:1
CC(O)C N1=NNC=N1
R2: H, C

Not regioselective: alternative product is substituated at the N at position 1 instead of 2
Inversion of stereo chemistry at chiral centers

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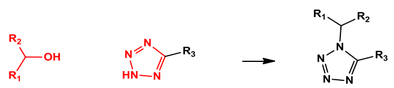
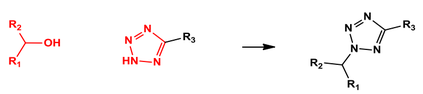


{Mitsunobu_tetrazole_3}
[C;H1&$(C([#6])[#6]),H2&$(C[#6]):1][OH1].[#7:2]1~[#7:3]~[#7H1:4]~[#7:5]~[#6:6]~1>>[C:1][#7H0:2]1:[#7:3]:[#7H0:4]:[#7:5]:[#6:6]:1
CC(O)C N1N=NC=N1
R2: H, C

Not regioselective: alternative product is substituated at the N at position 2 instead of 1
Inversion of stereo chemistry at chiral centers

40



{Mitsunobu_tetrazole_4}
[C;H1&$(C([#6])[#6]),H2&$(C[#6]):1][OH1].[#7:2]1~[#7:3]~[#7H1:4]~[#7:5]~[#6:6]~1>>[#7:2]1:[#7:3]:[#7:4]([C:1]):[#7:5]:[#6:6]:1
CC(O)C N1N=NC=N1
R2: H, C

Not regioselective: alternative product is substituated at the N at position 1 instead of 2
Inversion of stereo chemistry at chiral centers

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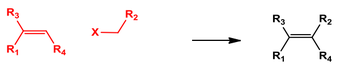
{Heck_terminal_vinyl}
[#6;c,$(C(=O)O),$(C#N):3][#6;H1:2]=[#6;H2:1].[#6;$([#6]=[#6]),$(c:c):4][Cl,Br,I]>>[#6:4]/[#6:1]=[#6:2]/[#6:3]
c1ccccc1C=C c1ccccc1Br
R1: aryl,COO,CN (electr. withdrawing groups -> trans selectivity)
R2: aryl, vinyl; X: Cl, Br, I

42



{Heck_non-terminal_vinyl}
[#6;c,$(C(=O)O),$(C#N):3][#6:2]([#6:5])=[#6;H1;$([#6][#6]):1].[#6;$([#6]=[#6]),$(c:c):4][Cl,Br,I]>>[#6:4][#6;H0:1]=[#6:2]([#6:5])[#6:3]
c1ccccc1C(C)=CC c1ccccc1Br
R1: aryl,COO,CN; R2: aryl, vinyl
X: Cl, Br, I; R3,4: C

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{Stille}
[#6;$(C=C-[#6]),$(c:c):1][Br,I].[Cl,Br,I][c:2]>>[c:2][#6:1]
c1ccccc1Br c1ccccc1Br
R1: vinyl (C=C), aryl; X1: Br,I
Ar: any aromatic system; X2: Cl, Br, I

Additional step: educt 1 has to be transformed into an organotin (stannane) first

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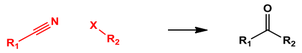
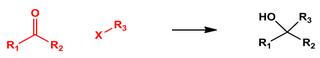


{Grignard_carbonyl}
[#6:1][C:2]#[#7;D1].[Cl,Br,I][#6;$([#6]~[#6]);!$([#6]([Cl,Br,I])[Cl,Br,I]);!$([#6]=O):3]>>[#6:1][C:2](=O)[#6:3]
CC#N CCBr
R2: aryl, alkyl
X: Cl, Br, I

Additional step: educt 2 has to be transformed into Grignard reagent (RMgX) first

45



{Grignard_alcohol}
[#6:1][C;H1,$([C]([#6])[#6]):2]=[OD1:3].[Cl,Br,I][#6;$([#6]~[#6]);!$([#6]([Cl,Br,I])[Cl,Br,I]);!$([#6]=O):4]>>[C:1][#6:2]([OH1:3])[#6:4]
CC(=O)C CCBr
R2: H, C
X: Cl, Br, I
Possible generation of stereo center
Additional step: educt 2 has to be transformed into Grignard reagent (RMgX) first

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{Sonogashira}
[#6;$(C=C-[#6]),$(c:c):1][Br,I].[CH1;$(C#CC):2]>>[#6:1][C:2]
c1cc(Br)ccc1 CC#C
R1: aryl, vinyl; X: Br, I
R2: any C

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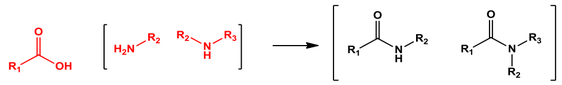
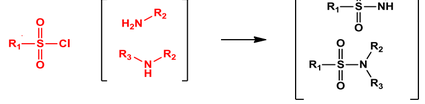


{Schotten-Baumann_amide}
[C;$(C=O):1][OH1].[N;$(N[#6]);!$(N=*);!$([N-]);!$(N#*);!$([ND3]);!$([ND4]);!$(N[O,N]);!$(N[C,S]=[S,O,N]):2]>>[C:1][N+0:2]
CC(=O)O NCC
R1,2,3: aryl allowed

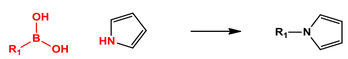
Additional step: activation of carboxy group (COOH -> COCl)

48



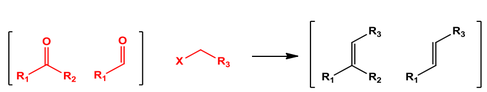
{sulfon_amide}
[S;$(S(=O)(=O)[C,N]):1][Cl].[N;$(NC);!$(N=*);!$([N-]);!$(N#*);!$([ND3]);!$([ND4]);!$(N[c,O]);!$(N[C,S]=[S,O,N]):2]>>[S:1][N+0:2]
CS(=O)(=O)Cl NCC
R1: C,N

49



{N-arylation_heterocycles}
[c:1]B(O)O.[nH1;+0;r5;!$(n[#6]=[O,S,N]);!$(n~n~n);!$(n~n~c~n);!$(n~c~n~n):2]>>[c:1][n:2]
c1ccccc1B(O)O N1C=NC=C1
R1: aryl
various 5-membered aromatic rings with NH and max. 2 N match, also those fused to other rings; see Lam et al, Tetrahedron Letters 39 (1998), p. 2941-2944
In case different protomers of the 5-membered heterocycle (differing in the position of NH) exist, regioisomers are likely to be produced

50



{Wittig}
[#6:3]-[C;H1,$([CH0](-[#6])[#6]);!$(CC=O):1]=[OD1].[Cl,Br,I][C;H2;$(C-[#6]);!$(CC[I,Br]);!$(CCO[CH3]):2]>>[C:3][C:1]=[C:2]
CC(=O)C BrCC
R1,R2: aryl, alkyl, vinyl, many functional groups are tolerated (March, page 1371); X: Cl, Br, I
only primary alkyl halides allowed here, although some secondary are reported; R3: carbon, not attached to Br,I or OMet, since they are good leaving groups which leads to elimination and the ylide will not be formed
Not stereo selective: E/Z isomers will likely be formed. Reaction conditions and substituents can push the reaction towards either isomer.
Additional step: Formation of the ylide from the alkyl halide by adding a triaryl phosphine

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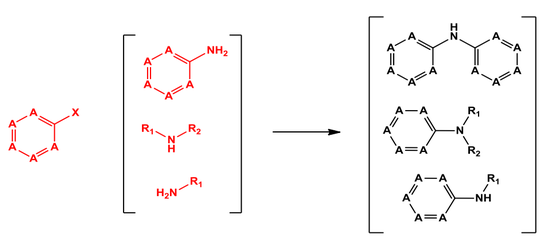

{Buchwald-Hartwig}
[Cl,Br,I][c;$(c1:[c,n]:[c,n]:[c,n]:[c,n]:[c,n]:1):1].[N;$(NC)&!$(N=*)&!$([N-])&!$(N#*)&!$([ND3])&!$([ND4])&!$(N[c,O])&!$(N[C,S]=[S,O,N]),H2&$(Nc1:[c,n]:[c,n]:[c,n]:[c,n]:[c,n]:1):2]>>[c:1][N:2]
c1ccccc1Br CNC
X: Cl, Br, I; A: N, C

R1,R2: alkyl (see March, page 877)

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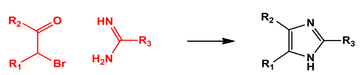
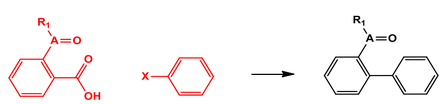


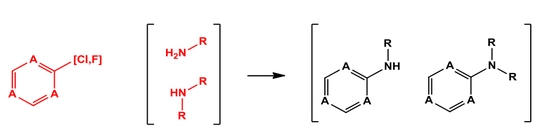
{imidazole}
[C;$(C([#6])[#6;!$([#6]Br)]):4](=[OD1])[CH;$(C([#6])[#6]):5]Br.[#7;H2:3][C;$(C(=N)(N)[c,#7]):2]=[#7;H1;D1:1]>>[C:4]1=[CH0:5][NH:3][C:2]=[N:1]1
CC(=O)C(Br)C N=C(N)NC
R1,R2: C
R3: aryl, N

53



{decarboxylative_coupling}
[c;$(c1[c;$(c[C,S,N](=[OD1])[*;R0;!OH1])]cccc1):1][C;$(C(=O)[O;H1])].[c;$(c1aaccc1):2][Cl,Br,I]>>[c:1][c:2]
c1c(C(=O)O)c([N+](=O)[O-]) c1ccccc1Br
A: C, S, N (see Goossen et al., J. Am. Chem. Soc., 2007, 129 (15), pp 4824–4833)
X: Cl, Br, I

54



{heteroaromatic_nuc_sub}
[c;!$(c1ccccc1);$(c1[n,c]c[n,c]c[n,c]1):1][Cl,F].[N;$(NC);!$(N=*);!$([N-]);!$(N#*);!$([ND3]);!$([ND4]);!$(N[c,O]);!$(N[C,S]=[S,O,N]):2]>>[c:1][N:2]
c1cnc(F)cc1 CN
A: C,N -> pyridine, pyrimidine and triazine. Heteroatoms activate the para and ortho positions for substitution
see March page 869 and supplement of Schuerer et al., 2005, JCIM 45,239-248

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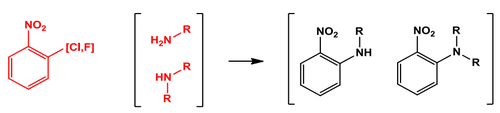

{nucl_sub_aromatic_ortho_nitro}
[c;$(c1c(N(~O)~O)cccc1):1][Cl,F].[N;$(NC);!$(N=*);!$([N-]);!$(N#*);!$([ND3]);!$([ND4]);!$(N[c,O]);!$(N[C,S]=[S,O,N]):2]>>[c:1][N:2]
c1c([N+](=O)[O-])c(F)ccc1 CN
ortho nitro groups have activating effect on nuc. substitution
see March page 869 and supplement of Schuerer et al., 2005, JCIM 45,239-248

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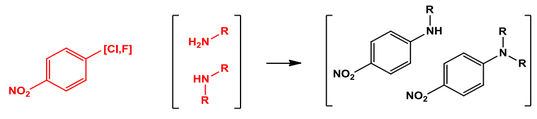

{nucl_sub_aromatic_para_nitro}
[c;$(c1ccc(N(~O)~O)cc1):1][Cl,F].[N;$(NC);!$(N=*);!$([N-]);!$(N#*);!$([ND3]);!$([ND4]);!$(N[c,O]);!$(N[C,S]=[S,O,N]):2]>>[c:1][N:2]
c1c(F)ccc([N+](=O)[O-])c1 CN
para nitro groups have activating effect on nuc. substitution

see March page 869 and supplement of Schuerer et al., 2005, JCIM 45,239-248

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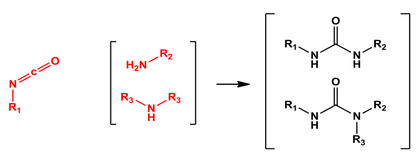
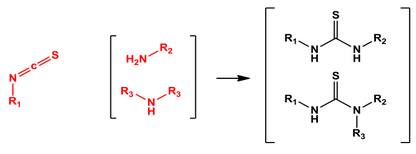


{urea}
[N;$(N-[#6]):3]=[C;$(C=O):1].[N;$(N[#6]);!$(N=*);!$([N-]);!$(N#*);!$([ND3]);!$([ND4]);!$(N[O,N]);!$(N[C,S]=[S,O,N]):2]>>[N:3]-[C:1]-[N+0:2]
CN=C=O CN
R1,2,3: C, aryl, alkyl

58



{thiourea}
[N;$(N-[#6]):3]=[C;$(C=S):1].[N;$(N[#6]);!$(N=*);!$([N-]);!$(N#*);!$([ND3]);!$([ND4]);!$(N[O,N]);!$(N[C,S]=[S,O,N]):2]>>[N:3]-[C:1]-[N+0:2]
CN=C=S CN
R1,2,3: C, aryl, alkyl