

# Paths of analysis\*

Analysis 2

Synthia

March 3, 2022

## 1 Analysis parameters

**Analysis type:** Automatic Retrosynthesis

**Rules:** none selected

**Filters:** FGI, FGI with protections

**Max. paths returned:** 5

**Max. iterations:** 300

**Commercial:**

1. Max. molecular weight - 1000 g/mol
2. Max. price - 1000 \$/g

**Published:**

1. Max. molecular weight - 1000 g/mol
2. Popularity - 10

**My Stockroom:**

1. Max. molecular weight - 1000 g/mol

**Reaction scoring formula:**  $\text{TUNNEL\_COEF} * \text{FGI\_COEF} * \text{STEP} * 20 + 1000000 * (\text{CONFLICT} + \text{NON\_SELECTIVITY} + \text{FILTERS} + \text{PROTECT})$

**Chemical scoring formula:**  $\text{SMALLER}^3, \text{SMALLER}^{1.5}$

**Min. search width:** 400

**Max. reactions per product:** 60

**Strategies:** none selected

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\*The results stated herein were generated using the proprietary platform owned and maintained by Grzybowski Scientific Inventions, Inc., a subsidiary of Merck KGaA, Darmstadt Germany. The results are provided on an as is basis, and shall be used solely in connection with the rights afforded in the license agreement and for no other purpose.

FGI Coeff: 0

JSON Parameters: {}

## 2 Paths

3 paths found. *Paths are sorted by score. Reactions are sorted in appearance order for each path.*

### 2.1 Path 1

Score: 77.96

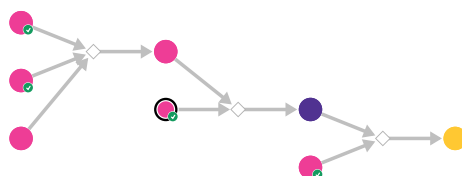
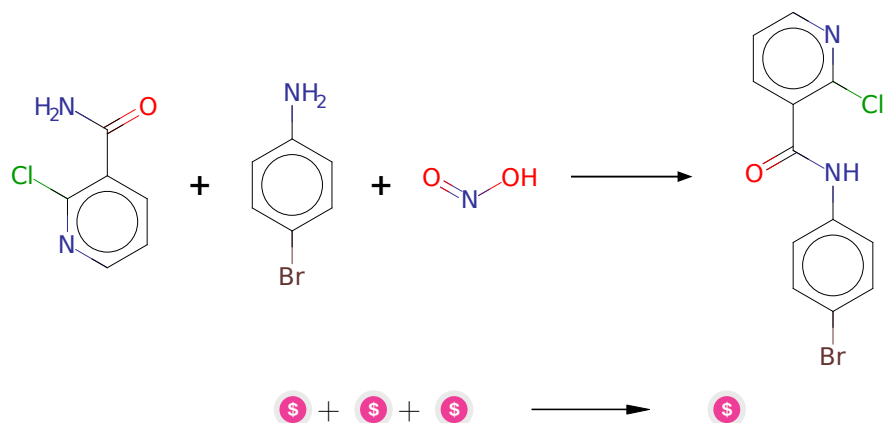


Figure 1: Outline of path 1

#### 2.1.1 Synthesis of N-arylamides from arenediazonium salts



Substrates:

1. 4-Bromoaniline - *available at Sigma-Aldrich*
2. Calcium nitrite solution - *available at Sigma-Aldrich*
3. 2-Chloronicotinamide - *Combi-Blocks*

Products:

1. n-(4-bromo-phenyl)-2-chloro-nicotinamide - *Enamine*

**Typical conditions:** 1) HCl.NaNO<sub>2</sub> 2) CuI.TBAI.N,N'-dimethylethane-1,2-diamine.K<sub>2</sub>CO<sub>3</sub>.DMSO.110C

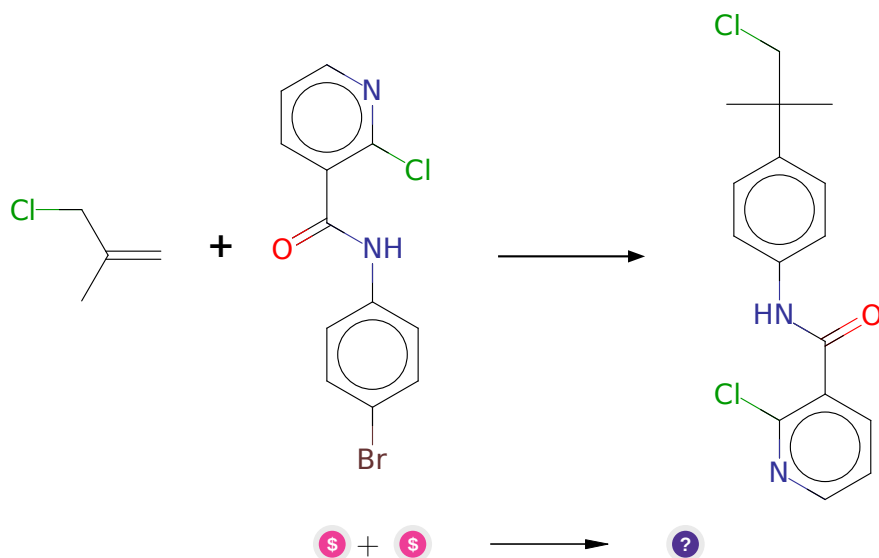
**Protections:** none

**Yield:** moderate

Reference: DOI: [10.1055/s-0034-1378556](https://doi.org/10.1055/s-0034-1378556)

Retrosynthesis ID: 1922

### 2.1.2 Pd-catalyzed coupling of aryl bromides and alkenes



**Substrates:**

1. n-(4-bromo-phenyl)-2-chloro-nicotinamide - *Enamine*
2. b-Methallyl chloride - *available at Sigma-Aldrich*

### Products:

1. CC(C)(CCl)c1ccc(NC(=O)c2cccnc2Cl)cc1

**Typical conditions:** [Pd(P(o-tol)3OAc]2.NaOCHO.TBAB.TEA

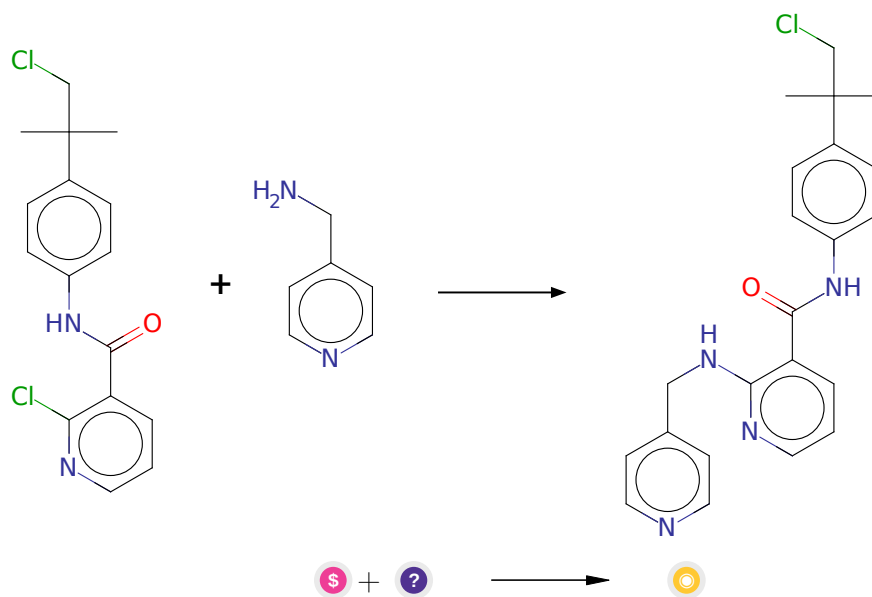
**Protections:** none

**Yield:** moderate

Reference: DOI: [10.1038/nature05569](https://doi.org/10.1038/nature05569)

Retrosynthesis ID: 8840

### 2.1.3 Buchwald-Hartwig amination



#### Substrates:

1. 4-Picolylamine - *available at Sigma-Aldrich*
2. CC(C)(CCl)c1ccc(NC(=O)c2cccnc2Cl)cc1

#### Products:

1. CC(C)(CCl)c1ccc(NC(=O)c2cccnc2NCc3ccncc3)cc1

**Typical conditions:** PdCl<sub>2</sub>.NaOtBu.dioxane.heat

**Protections:** none

**Yield:** good

**Reference:** [10.1021/acs.oprd.9b00161](#) and [10.1002/anie.201904795](#) and [10.1021/acs.chemrev.6b00512](#)

Retrosynthesis ID: 10319

## 2.2 Path 2

Score: 112.45

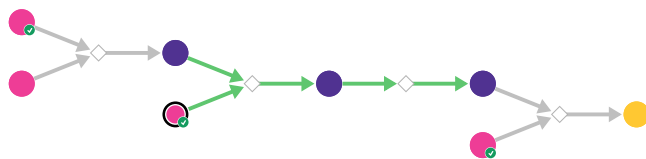
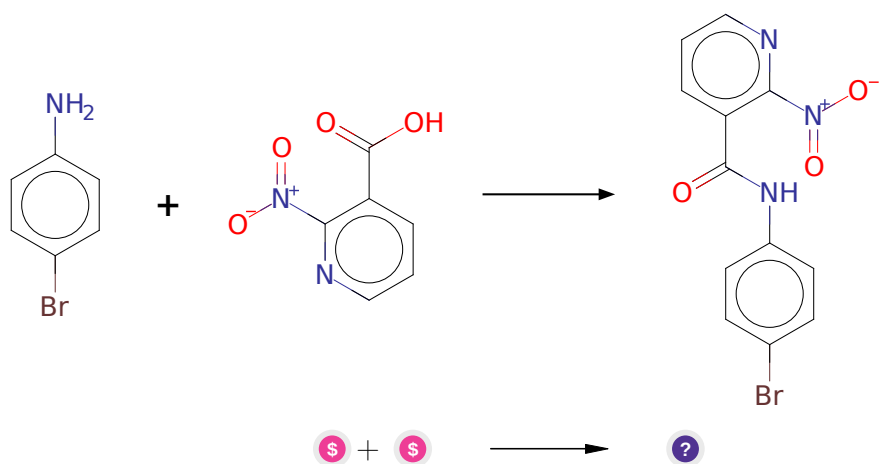


Figure 2: Outline of path 2

### 2.2.1 Amide coupling



#### Substrates:

1. 4-Bromoaniline - *available at Sigma-Aldrich*
2. 2-Nitronicotinic acid - *Combi-Blocks*

#### Products:

1. O=C(Nc1ccc(Br)cc1)c1cccnc1[N+](=O)[O-]

**Typical conditions:** DCC.DCM or EDC.DCM or SOCl<sub>2</sub>.DCM

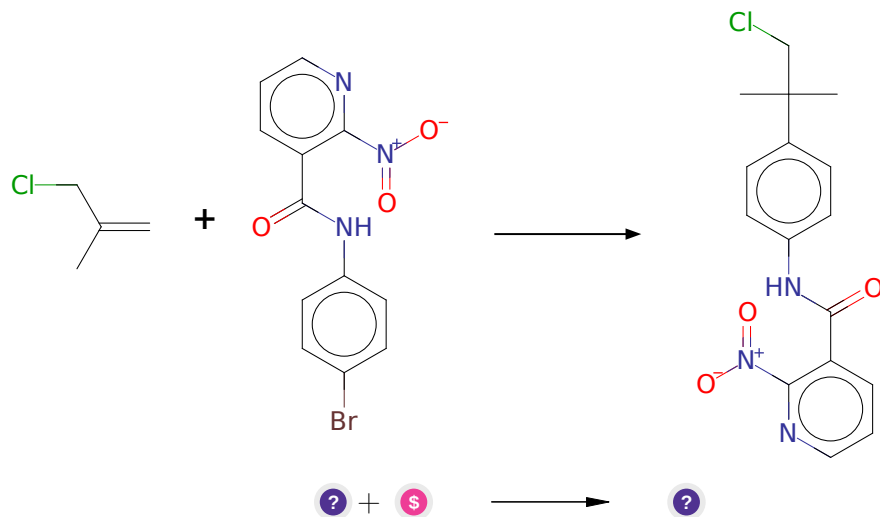
**Protections:** none

**Yield:** good

**Reference:** [10.1021/cr100048w](#) and [10.1039/B701677H](#) and [10.1039/C5RA24527C](#) and [10.3727/000000006783981206](#) and [10.1021/np060007f](#) and [10.1021/jo00012a058](#) and [10.1016/j.bmcl.2007.08.037](#) and [10.1039/C0OB00355G](#) and [10.1021/jm500031w](#) (p.3056) and [10.1016/j.tet.2011.03.046](#)

**Retrosynthesis ID:** 28548

### 2.2.2 Pd-catalyzed coupling of aryl bromides and alkenes



#### Substrates:

1. O=C(Nc1ccc(Br)cc1)c1cccnc1[N+](=O)[O-]
2. b-Methallyl chloride - *available at Sigma-Aldrich*

#### Products:

1. CC(C)(CCl)c1ccc(NC(=O)c2cccnc2[N+](=O)[O-])cc1

**Typical conditions:** [Pd(P(o-tol)3OAc]2.NaOCHO.TBAB.TEA

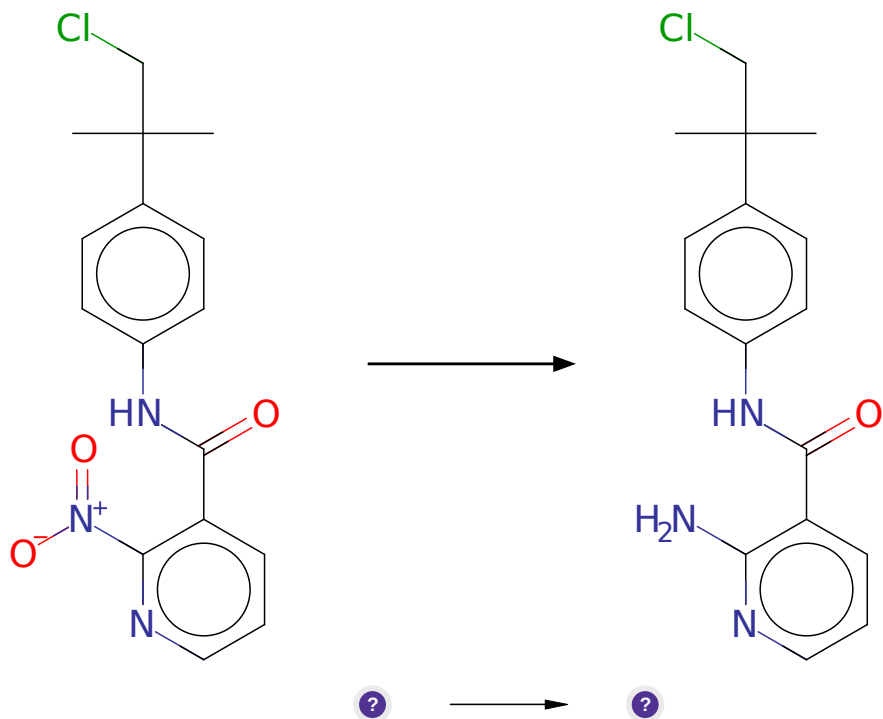
**Protections:** none

**Yield:** moderate

**Reference:** DOI: [10.1038/nature05569](https://doi.org/10.1038/nature05569)

**Retrosynthesis ID:** 8840

### 2.2.3 Palladium-catalyzed reduction of nitro group



**Substrates:**

1. CC(C)(CCl)c1ccc(NC(=O)c2cc[n+]([O-])cc2[nH])cc1

**Products:**

1. CC(C)(CCl)c1ccc(NC(=O)c2cc[nH]c(N)c2)cc1

**Typical conditions:** H<sub>2</sub>.Pd/C

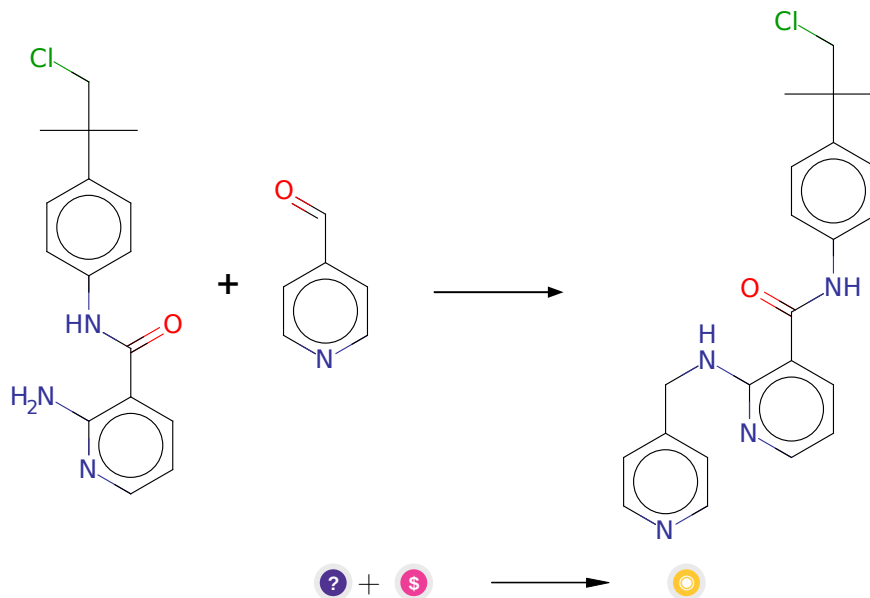
**Protections:** none

**Yield:** moderate

**Reference:** DOI: [10.1002/anie.200501738](https://doi.org/10.1002/anie.200501738) and [10.1002/anie.200352175](https://doi.org/10.1002/anie.200352175) and [10.1016/j.tetlet.2015.05.004](https://doi.org/10.1016/j.tetlet.2015.05.004) and [10.3390/molecules13061427](https://doi.org/10.3390/molecules13061427) and [10.1016/S0968-0896\(03\)00459-0](https://doi.org/10.1016/S0968-0896(03)00459-0)

**Retrosynthesis ID:** 29908

### 2.2.4 Synthesis of secondary amines



#### Substrates:

1. CC(C)(CCl)c1ccc(NC(=O)c2cccnc2N)cc1
2. Isonicotinaldehyde - *available at Sigma-Aldrich*

#### Products:

1. CC(C)(CCl)c1ccc(NC(=O)c2cccnc2NCc3ccncc3)cc1

**Typical conditions:** sodium triacetoxyborohydride.dichloromethane

**Protections:** none

**Yield:** good

**Reference:** DOI: [10.1021/ed077p270](https://doi.org/10.1021/ed077p270)

**Retrosynthesis ID:** 245716

## 2.3 Path 3

**Score:** 119.74



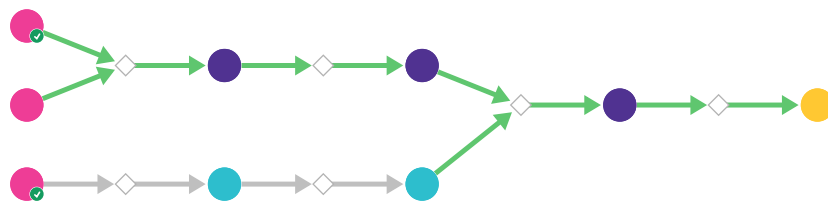
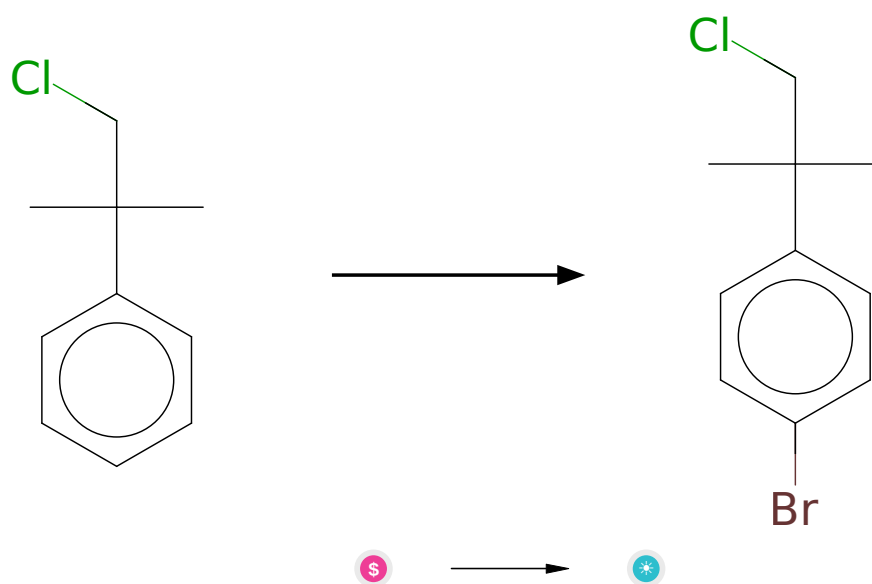


Figure 3: Outline of path 3

### 2.3.1 Bromination of aromatic compounds



#### Substrates:

1. Neophyl chloride - *available at Sigma-Aldrich*

#### Products:

1. p-brom-(chlor-tert-butyl)-benzol

**Typical conditions:** Br<sub>2</sub>.Fe

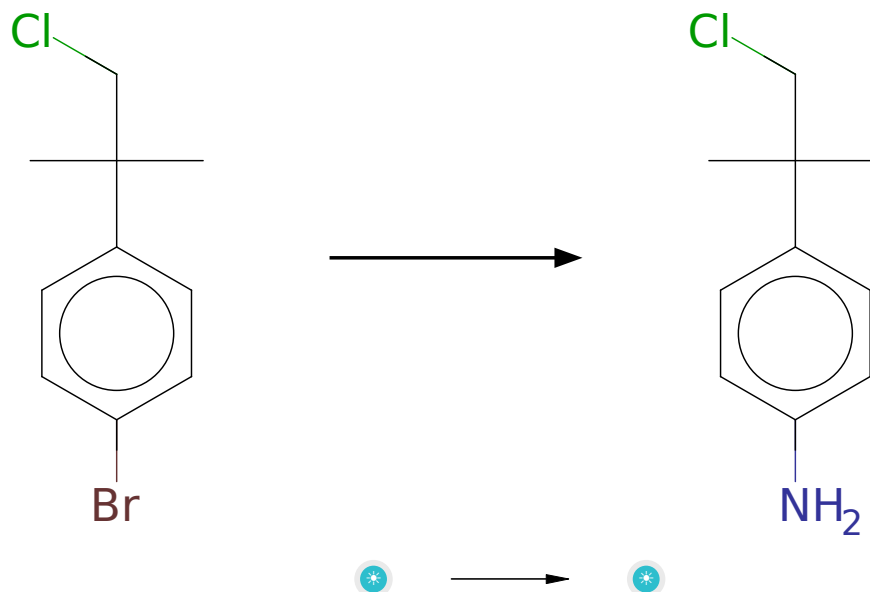
**Protections:** none

**Yield:** good

**Reference:** *10.1021/acs.accounts.6b00120*

**Retrosynthesis ID:** 7777000

### 2.3.2 Amination of aryl bromides



**Substrates:**

1. p-brom-(chlor-tert-butyl)-benzol

**Products:**

1. p-(1-chloro-2-methyl-2-propyl)aniline

**Typical conditions:** Pd.ligand.base or CuI.ligand.base

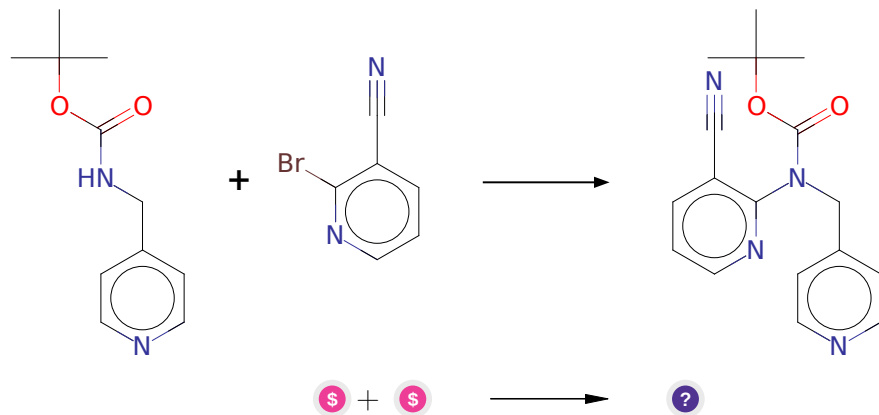
**Protections:** none

**Yield:** good

**Reference:** [10.1021/ja903049z](#) and [10.1021/jo060945k](#) and [10.1021/jo060190h](#) and [10.1039/B923255A](#) and [10.1021/jm8003625](#) and [10.1021/jo9006738](#)

**Retrosynthesis ID:** 28544

### 2.3.3 Arylation of carbamates with aryl bromides



#### Substrates:

1. N-Boc-4-aminomethylpyridine - *available at Sigma-Aldrich*
2. 2-Bromonicotinonitrile - *Combi-Blocks*

#### Products:

1. CC(C)(C)OC(=O)N(Cc1ccncc1)c1ncccc1C#N

**Typical conditions:** Base.[Pd].catalyst.dioxane.heat or  
CuI.diamine.base.DMF.heat

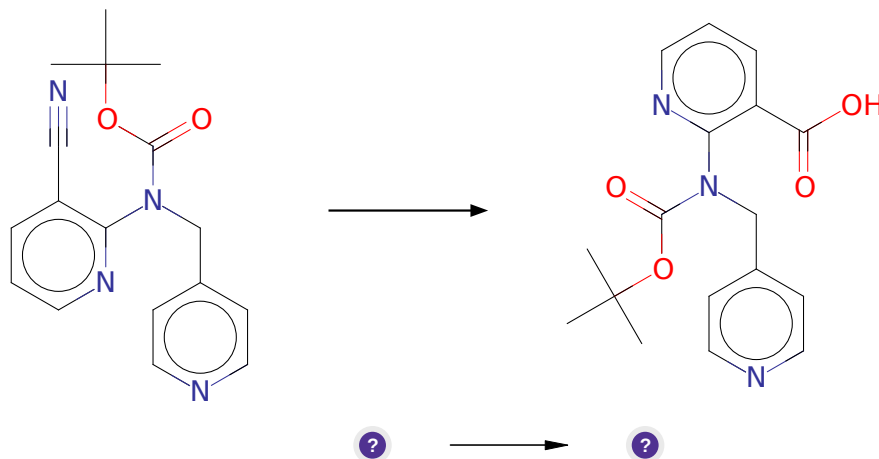
**Protections:** none

**Yield:** good

**Reference:** [10.1016/j.tetlet.2014.03.016](#) and [10.1021/ja012610k](#) and  
[10.1021/ol016208m](#) and [10.1021/ol502322c](#)

**Retrosynthesis ID:** 10012542

### 2.3.4 Base hydrolysis of nitriles to carboxylic acids



**Substrates:**

1. CC(C)(C)OC(=O)N(Cc1ccncc1)c1ncccc1C#N

**Products:**

1. CC(C)(C)OC(=O)N(Cc1ccncc1)c1ncccc1C(=O)O

**Typical conditions:** NaOH.heating.H<sub>2</sub>O

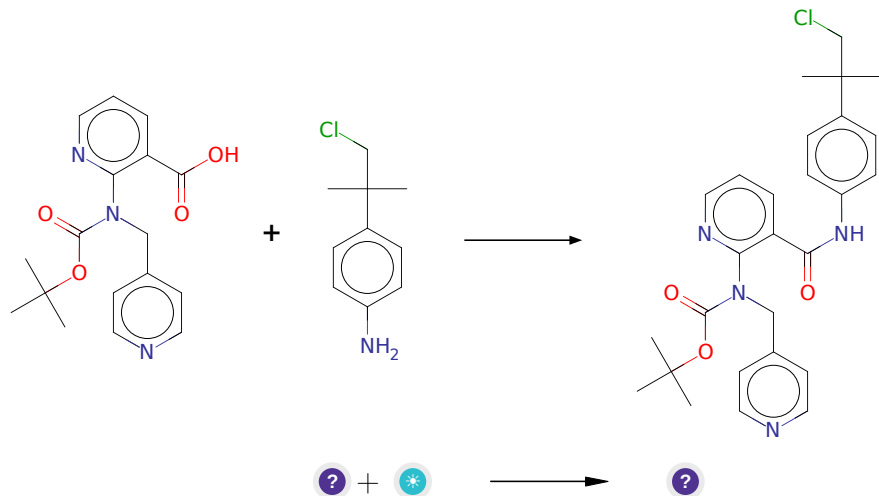
**Protections:** none

**Yield:** moderate

**Reference:** [10.1002/1099-0690\(200111\)2001:22<4207::AID-EJOC4207>3.0.CO;2-3](#) and [10.1021/acs.jmedchem.5b00702](#) and [10.1016/j.bmc.2011.07.045](#)

**Retrosynthesis ID:** 15107

### 2.3.5 Amide coupling



#### Substrates:

1. CC(C)(C)OC(=O)N(Cc1ccncc1)c1ncccc1C(=O)O
2. p-(1-chloro-2-methyl-2-propyl)aniline

#### Products:

1. CC(C)(C)OC(=O)N(Cc1ccncc1)c1ncccc1C(=O)Nc1ccc(C(C)(C)CCl)cc1

**Typical conditions:** DCC.DCM or EDC.DCM or SOCl<sub>2</sub>.DCM

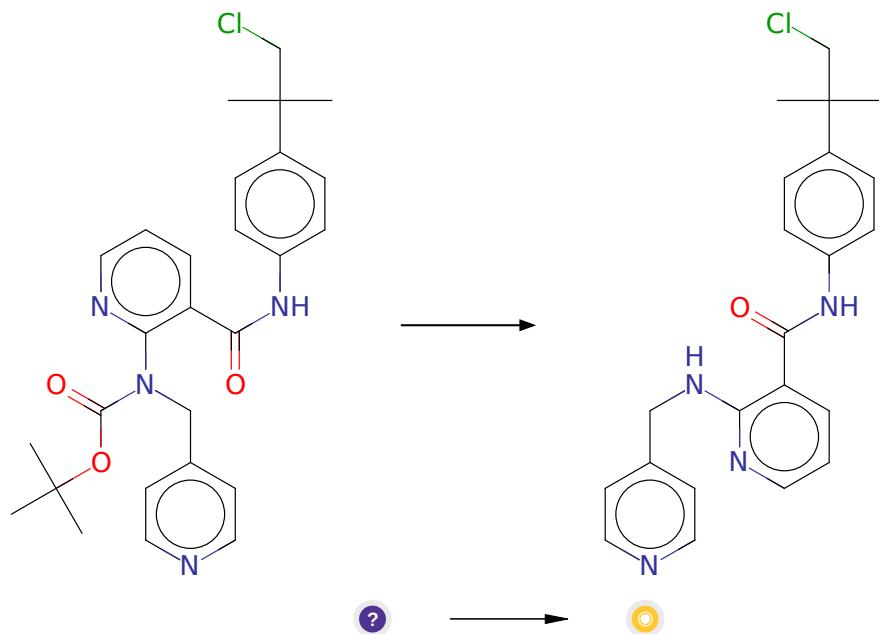
**Protections:** none

**Yield:** good

**Reference:** [10.1021/cr100048w](#) and [10.1039/B701677H](#) and [10.1039/C5RA24527C](#) and [10.3727/000000006783981206](#) and [10.1021/np060007f](#) and [10.1021/jo00012a058](#) and [10.1016/j.bmcl.2007.08.037](#) and [10.1039/C0OB00355G](#) and [10.1021/jm500031w](#) (p.3056) and [10.1016/j.tet.2011.03.046](#)

**Retrosynthesis ID:** 28548

### 2.3.6 Boc removal



#### Substrates:

1. CC(C)(C)OC(=O)N(Cc1ccncc1)c1ncccc1C(=O)Nc1ccc(C(C)(C)CCl)cc1

#### Products:

1. CC(C)(CCl)c1ccc(NC(=O)c2cccnc2NCc2ccncc2)cc1

**Typical conditions:** TFA.DCM

**Protections:** none

**Yield:** good

**Reference:** [10.1016/j.bmc.2015.11.006](https://doi.org/10.1016/j.bmc.2015.11.006) and [10.1021/jo047752m](https://doi.org/10.1021/jo047752m) and [10.1016/j.tetlet.2007.09.003](https://doi.org/10.1016/j.tetlet.2007.09.003)

**Retrosynthesis ID:** 10025811