Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Supplementary Information for Manuscript

The logic of translating chemical knowledge into machine-processable forms: A modern playground for physical-organic chemistry.

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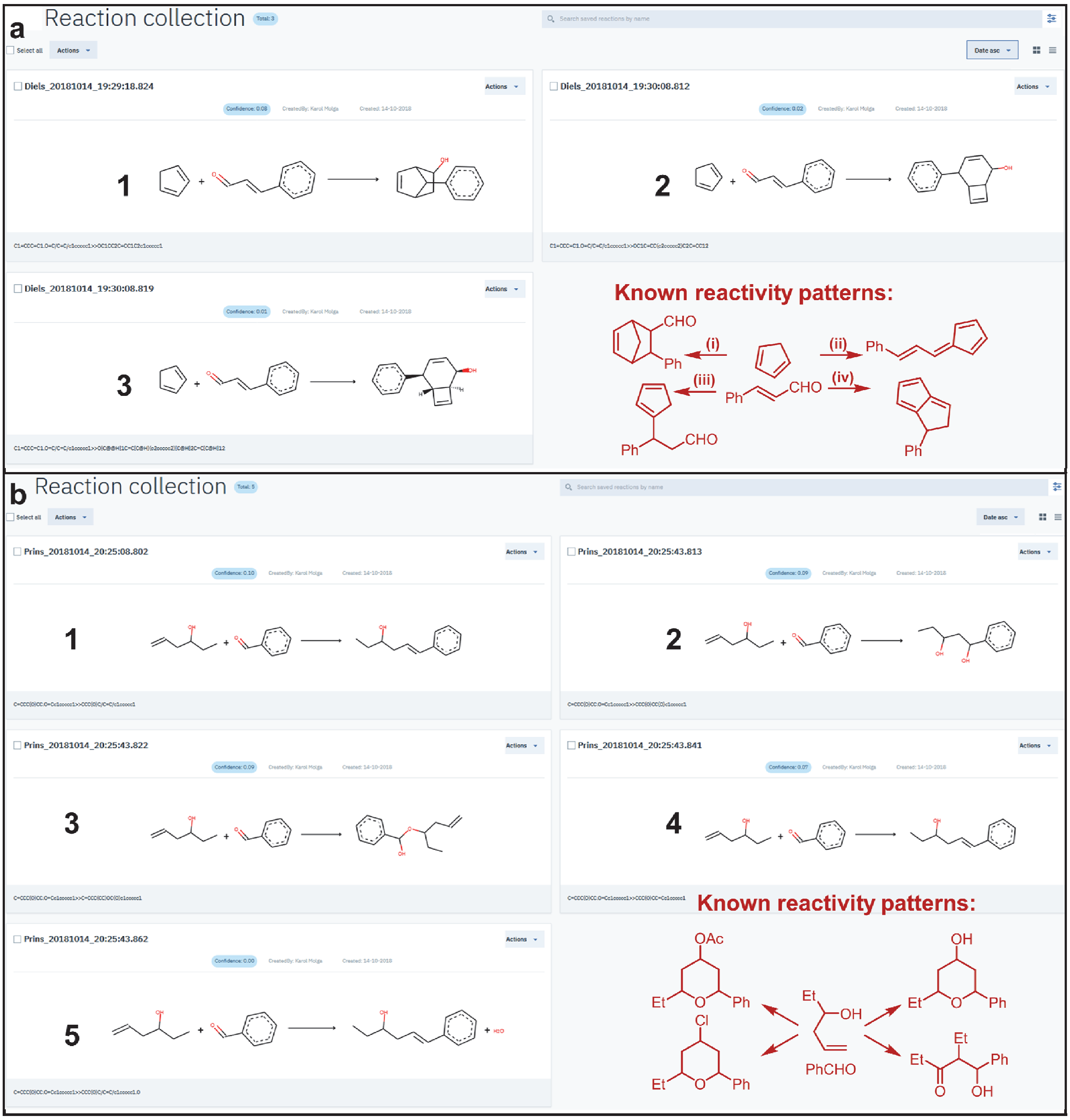
Contents:

Examples of synthetic predictions by linguistics-based (**Figure S1**) and machine-extracted, rule-based (**Figures S2-S25**) algorithms vs. predictions by Chematica (**Figures S2-S25**) using mechanism-based reaction rules. The examples are chosen to emphasize the difference in rule quality when dealing with even simple targets. For more complex synthetic examples using Chematica, see ref. 7 and the experimentally validated syntheses in ref. 9 in the main text. The examples are based on the versions of the softwares as of late October 2018.



☐ Diels_20181014_19:29:18.824
Confidence: 0.08 CreatedBy: Karol Molga Created: 14-10-2018

```
C1=CCC=C1.O=C/C=C/c1ccccc1>>OC1CC2C=CC1C2c1ccccc1
```

☐ Diels_20181014_19:30:08.812
Confidence: 0.02 CreatedBy: Karol Molga Created: 14-10-2018

```
C1=CCC=C1.O=C/C=C/c1ccccc1>>OC1C=CC(c2ccccc2)C2C=CC12
```

☐ Diels_20181014_19:30:08.819
Confidence: 0.01 CreatedBy: Karol Molga Created: 14-10-2018

```
C1=CCC=C1.O=C/C=C/c1ccccc1>>O[C@@H]1C=C[C@H](c2ccccc2)[C@H]2C=C[C@H]12
```

☐ Prins_20181014_20:25:08.802
Confidence: 0.10 CreatedBy: Karol Molga Created: 14-10-2018

```
C=CCC(O)CC.O=Cc1ccccc1>>CCC(O)C/C=C/c1ccccc1
```

☐ Prins_20181014_20:25:43.813
Confidence: 0.09 CreatedBy: Karol Molga Created: 14-10-2018

```
C=CCC(O)CC.O=Cc1ccccc1>>CCC(O)CC(O)c1ccccc1
```

☐ Prins_20181014_20:25:43.822
Confidence: 0.09 CreatedBy: Karol Molga Created: 14-10-2018

```
C=CCC(O)CC.O=Cc1ccccc1>>C=CCC(CC)OC(O)c1ccccc1
```

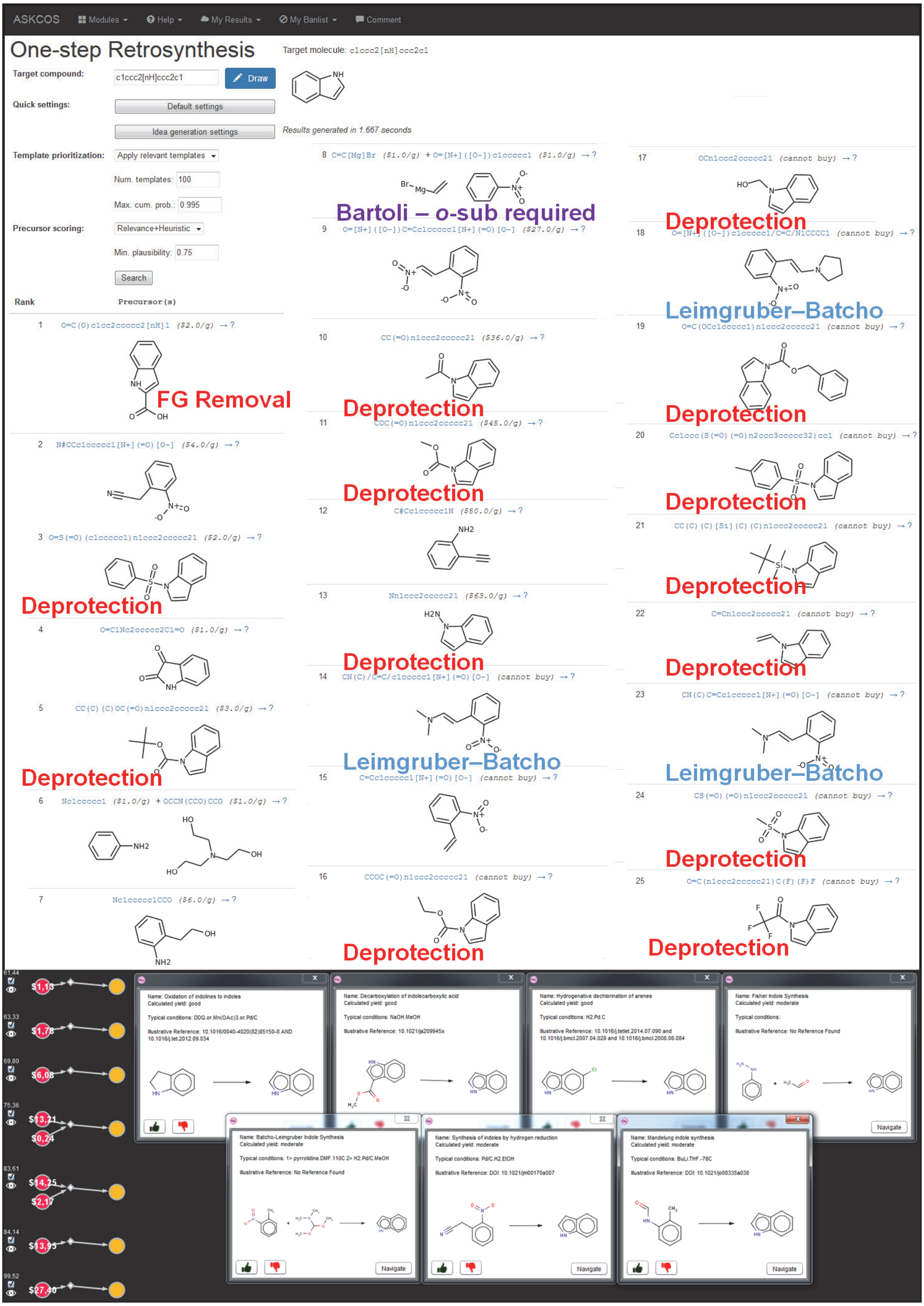
☐ Prins_20181014_20:25:43.841
Confidence: 0.07 CreatedBy: Karol Molga Created: 14-10-2018

```
C=CCC(O)CC.O=Cc1ccccc1>>CCC(O)CC=Cc1ccccc1
```

☐ Prins_20181014_20:25:43.862
Confidence: 0.00 CreatedBy: Karol Molga Created: 14-10-2018

```
C=CCC(O)CC.O=Cc1ccccc1>>CCC(O)C/C=C/c1ccccc1.O
```

Figure S1. IBM's tool (https://rxn.res.ibm.com) for predicting outcomes of organic reactions using neural sequence-to-sequence models (based on Schwaller *et. al.*, *Chem. Sci.*, **2018**, 9, 6091) fails even for simple examples. **a**) Neural network predictions for the reaction of cinnamaldehyde with cyclopentadiene are far from the known and realistic reactivity patterns. These two compounds are known to participate in Diels-Alder (i), aldol (ii), ene (iii) or tandem ene-aldol (iv) reactions shown in the red inset. None of these reactivity patterns are proposed. Instead, formation of products returned by the neural network requires extrusion of carbon atom from enal (#1) or migration of carbon atom from cyclopentadiene to enal to form 6-4 ring system in #2 and #3. Both processes proposed by the platform would raise an eyebrow (mildly speaking…) of any practicing organic chemist. **b)** Allyl alcohols are well known to react with aldehydes under acidic conditions yielding tetrahydropyrans in Prins reaction or under metal catalysis to deliver reductive aldol adducts (reactions shown in red in the inset). None of these reactivity patterns are rediscovered by IBM’s neural network. Instead, the proposed products are made via a highly improbable (unknown in chemistry!) coupling of alkene and aldehyde with the extrusion of carbon atoms from the unactivated alkyl chain yielding products with five (#2) and six carbon (#1,#4,#5) chains. (Additionally, #1, #4 and #5 return the same main product with different confidence levels). The only reasonable suggestion (albeit predicted as only third) is the formation of acyclic acetal. For this example, comparison to Chematica is not feasible since Chematica works in the retrosynthetic, not “forward” direction.



One-step Retrosynthesis

Target molecule: `c1ccc2[nH]ccc2c1`

Target compound: c1ccc2[nH]ccc2c1

Quick settings: Default settings | Idea generation settings

Template prioritization: Apply relevant templates

Num. templates: 100

Max. cum. prob.: 0.995

Precursor scoring: Relevance+Heuristic

Min. plausibility: 0.75

Results generated in 1.667 seconds

Rank	Precursor(s)
1	`O=C(O)c1cc2ccccc2[nH]1` ($2.0/g) → ?
2	`N#CCc1ccccc1[N+](=O)[O-]` ($4.0/g) → ?
3	`O=S(=O)(c1ccccc1)n1ccc2ccccc21` ($2.0/g) → ?
4	`O=C1Nc2ccccc2C1=O` ($1.0/g) → ?
5	`CC(C)(C)OC(=O)n1ccc2ccccc21` ($3.0/g) → ?
6	`Nc1ccccc1` ($1.0/g) + `OCCN(CCO)CCO` ($1.0/g) → ?
7	`Nc1ccccc1CCO` ($6.0/g) → ?
8	`C=C[Mg]Br` ($1.0/g) + `O=[N+]([O-])c1ccccc1` ($1.0/g) → ?
9	`O=[N+]([O-])C=Cc1ccccc1[N+](=O)[O-]` ($27.0/g) → ?
10	`CC(=O)n1ccc2ccccc21` ($36.0/g) → ?
11	`COC(=O)n1ccc2ccccc21` ($45.0/g) → ?
12	`C#Cc1ccccc1N` ($50.0/g) → ?
13	`Nn1ccc2ccccc21` ($63.0/g) → ?
14	`CN(C)/C=C/c1ccccc1[N+](=O)[O-]` (cannot buy) → ?
15	`C=Cc1ccccc1[N+](=O)[O-]` (cannot buy) → ?
16	`CCOC(=O)n1ccc2ccccc21` (cannot buy) → ?
17	`OCn1ccc2ccccc21` (cannot buy) → ?
18	`O=[N+]([O-])c1ccccc1/C=C/N1CCCC1` (cannot buy) → ?
19	`O=C(OCc1ccccc1)n1ccc2ccccc21` (cannot buy) → ?
20	`Cc1ccc(S(=O)(=O)n2ccc3ccccc32)cc1` (cannot buy) → ?
21	`CC(C)(C)[Si](C)(C)n1ccc2ccccc21` (cannot buy) → ?
22	`C=Cn1ccc2ccccc21` (cannot buy) → ?
23	`CN(C)C=Cc1ccccc1[N+](=O)[O-]` (cannot buy) → ?
24	`CS(=O)(=O)n1ccc2ccccc21` (cannot buy) → ?
25	`O=C(n1ccc2ccccc21)C(F)(F)F` (cannot buy) → ?

Name: Oxidation of indolines to indoles
Calculated yield: good
Typical conditions: DDQ.or.Mn(OAc)3.or.Pd/C
Illustrative Reference: 10.1016/0040-4020(82)85150-8 AND 10.1016/j.tet.2012.09.034

Name: Decarboxylation of indolecarboxylic acid
Calculated yield: good
Typical conditions: NaOH.MeOH
Illustrative Reference: 10.1021/ja209945x

Name: Hydrogenative dechlorination of arenes
Calculated yield: good
Typical conditions: H2.Pd.C
Illustrative Reference: 10.1016/j.tetlet.2014.07.090 and 10.1016/j.bmcl.2007.04.028 and 10.1016/j.bmcl.2008.08.084

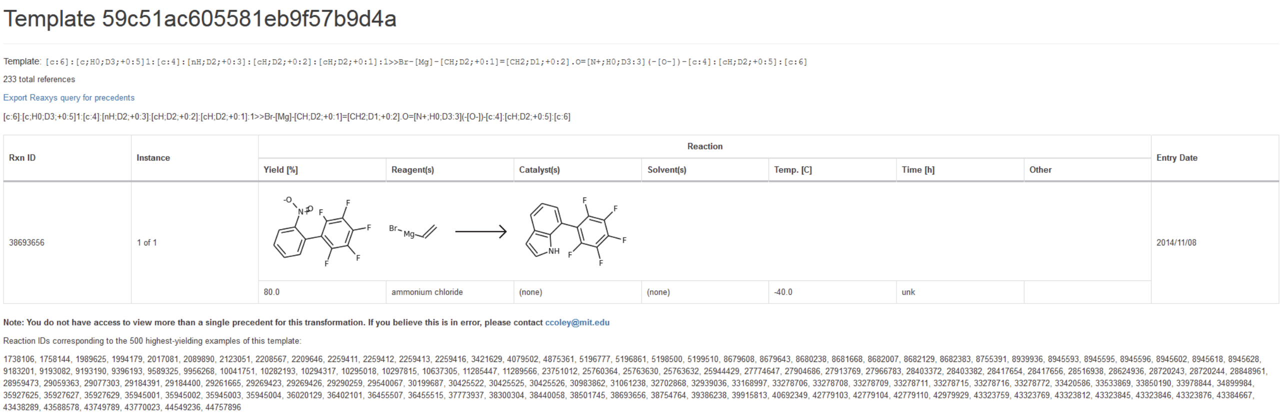
Name: Fisher Indole Synthesis
Calculated yield: moderate
Typical conditions:
Illustrative Reference: No Reference Found

Name: Batcho-Leimgruber Indole Synthesis
Calculated yield: moderate
Typical conditions: 1> pyrrolidine.DMF.110C 2> H2.Pd/C.MeOH
Illustrative Reference: No Reference Found

Name: Synthesis of indoles by hydrogen reduction
Calculated yield: moderate
Typical conditions: Pd/C.H2.EtOH
Illustrative Reference: DOI: 10.1021/jm00170a007

Name: Mandelung indole synthesis
Calculated yield: moderate
Typical conditions: BuLi.THF.-78C
Illustrative Reference: DOI: 10.1021/jo00335a038

Figure S2. A chemically trivial retrosynthetic analysis of indole's synthesis in MIT's ASKCOS system. The results obtained are mainly (14/25) deprotections or removals of functional groups, leading to commercially unavailable (8/14) or expensive (>30$/g, 3/14) predecessors. Additionally, the program produced two variants (#14 is identical with #23) of the same method – Leimgruber-Batcho cyclisation – with only minute differences in leaving groups (diethylamine vs. pyrrolidine). The proposed Bartoli indole synthesis requires *ortho*-substitution (which is missing in the examined case and in the extracted reaction core, see **Figure S3**) to proceed with any satisfactory yield – we note that such small nuances of chemical reactivity are extremely important as the small difference in structure may cause dramatic change in reactivity and virtually impossible to be covered by any automatic rule extraction system due to insufficient number of reported examples. The program also does not account for the pricing of starting materials and scores higher cyclisation of more expensive (4$/g) nitrophenylacetonitrile (#2) over similar reaction (#6) using aniline (1$/g) and tris-etanoloamine (1$/g) or reduction (#4) of indolinone (1$/g). Top 25 out of 32 returned results are shown. Top predictions returned by Chematica (bottom) take advantage of inexpensive and commercially available derivatives (indoline, methyl indole-3-carboxylate or chloroindole). Alternatively, the indole skeleton is created from the phenylacetonitrile or in the Fischer, Leimgruber-Batcho, or Mandelung processes.



Template 59c51ac605581eb9f57b9d4a

Template: `[c:6]:[c;H0;D3;+0:5]1:[c:4]:[nH;D2;+0:3]:[cH;D2;+0:2]:[cH;D2;+0:1]:1>>Br-[Mg]-[CH;D2;+0:1]=[CH2;D1;+0:2].O=[N+;H0;D3:3](-[O-])-[c:4]:[cH;D2;+0:5]:[c:6]`

233 total references

Export Reaxys query for precedents

[c:6]:[c;H0;D3;+0:5]1:[c:4]:[nH;D2;+0:3]:[cH;D2;+0:2]:[cH;D2;+0:1]:1>>Br-[Mg]-[CH;D2;+0:1]=[CH2;D1;+0:2].O=[N+;H0;D3:3](-[O-])-[c:4]:[cH;D2;+0:5]:[c:6]

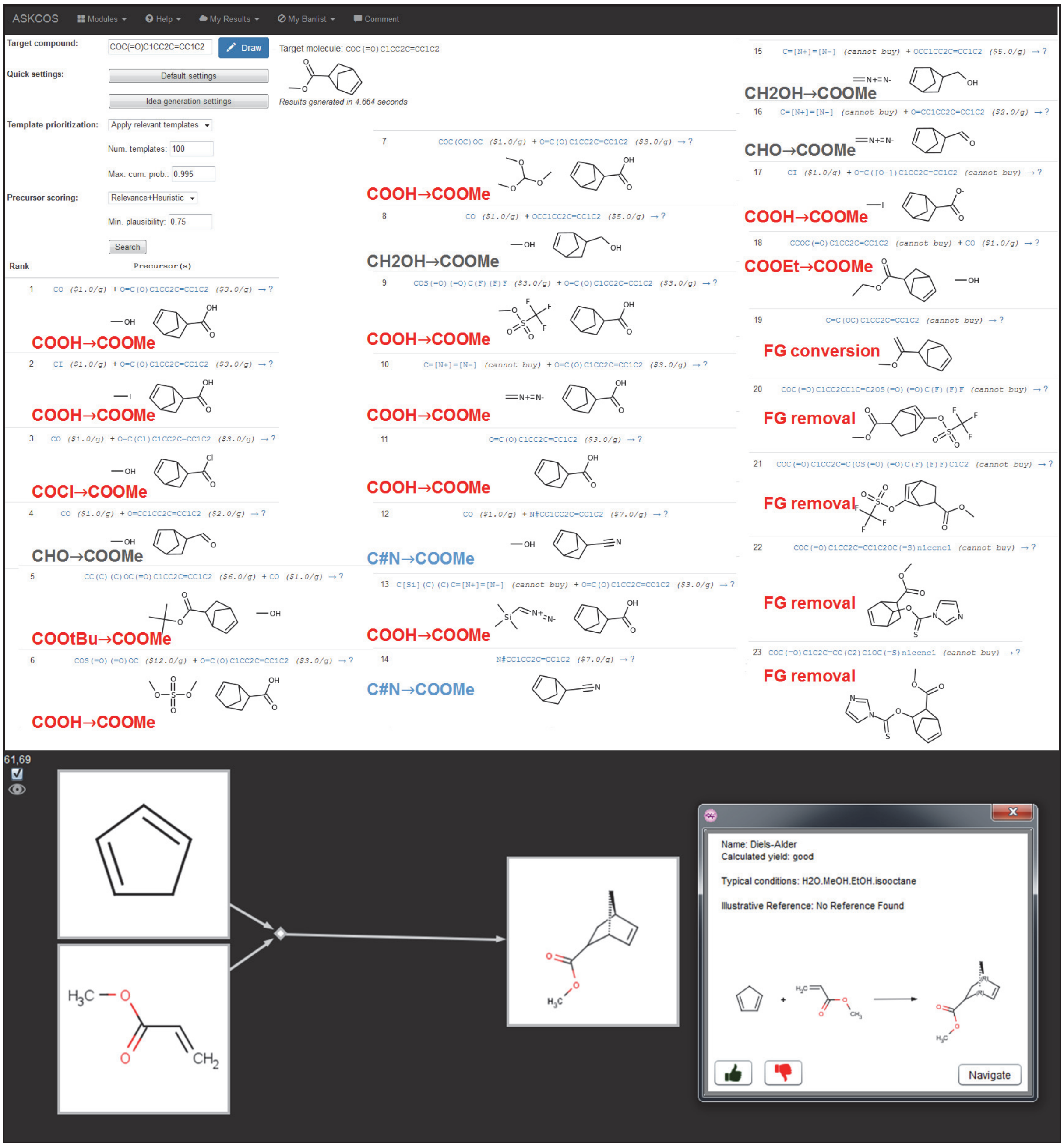
Rxn ID	Instance	Reaction							Entry Date
		Yield [%]	Reagent(s)	Catalyst(s)	Solvent(s)	Temp. [C]	Time [h]	Other	
38693656	1 of 1	80.0	ammonium chloride	(none)	(none)	-40.0	unk		2014/11/08

Note: You do not have access to view more than a single precedent for this transformation. If you believe this is in error, please contact ccoley@mit.edu

Reaction IDs corresponding to the 500 highest-yielding examples of this template:

1738106, 1758144, 1989625, 1994179, 2017081, 2089890, 2123051, 2208567, 2209646, 2259411, 2259412, 2259413, 2259416, 3421629, 4079502, 4875361, 5196777, 5196861, 5198500, 5199510, 8679608, 8679643, 8680238, 8681668, 8682007, 8682129, 8682383, 8755391, 8939936, 8945593, 8945595, 8945596, 8945602, 8945618, 8945628, 9183201, 9193082, 9193190, 9396193, 9589325, 9956268, 10041751, 10282193, 10294317, 10295018, 10297815, 10637305, 11285447, 11289566, 23751012, 25760364, 25763630, 25763632, 25944429, 27774647, 27904686, 27913769, 27966783, 28403372, 28403382, 28417654, 28417656, 28516938, 28624936, 28720243, 28720244, 28848961, 28959473, 29059363, 29077303, 29184391, 29184400, 29261665, 29269423, 29269426, 29290259, 29540067, 30199687, 30425522, 30425525, 30425526, 30983862, 31061238, 32702868, 32939036, 33168997, 33278706, 33278708, 33278709, 33278711, 33278715, 33278716, 33278772, 33420586, 33533869, 33850190, 33978844, 34899984, 35927625, 35927627, 35927629, 35945001, 35945002, 35945003, 35945004, 36020129, 36402101, 36455507, 36455515, 37773937, 38300304, 38440058, 38501745, 38693656, 38754764, 39386238, 39915813, 40692349, 42779103, 42779104, 42779110, 42979929, 43323759, 43323769, 43323812, 43323845, 43323846, 43323876, 43384667, 43438289, 43588578, 43749789, 43770023, 44549236, 44757896

Figure S3. Automatically extracted core of the Bartoli indole synthesis from the ASKCOS software. The necessary *ortho*-substitution is not taken into account.



Target compound: COC(=O)C1CC2C=CC1C2

Quick settings:

Template prioritization: Apply relevant templates

Num. templates: 100

Max. cum. prob.: 0.995

Precursor scoring: Relevance+Heuristic

Min. plausibility: 0.75

Target molecule: COC(=O)C1CC2C=CC1C2

Results generated in 4.664 seconds

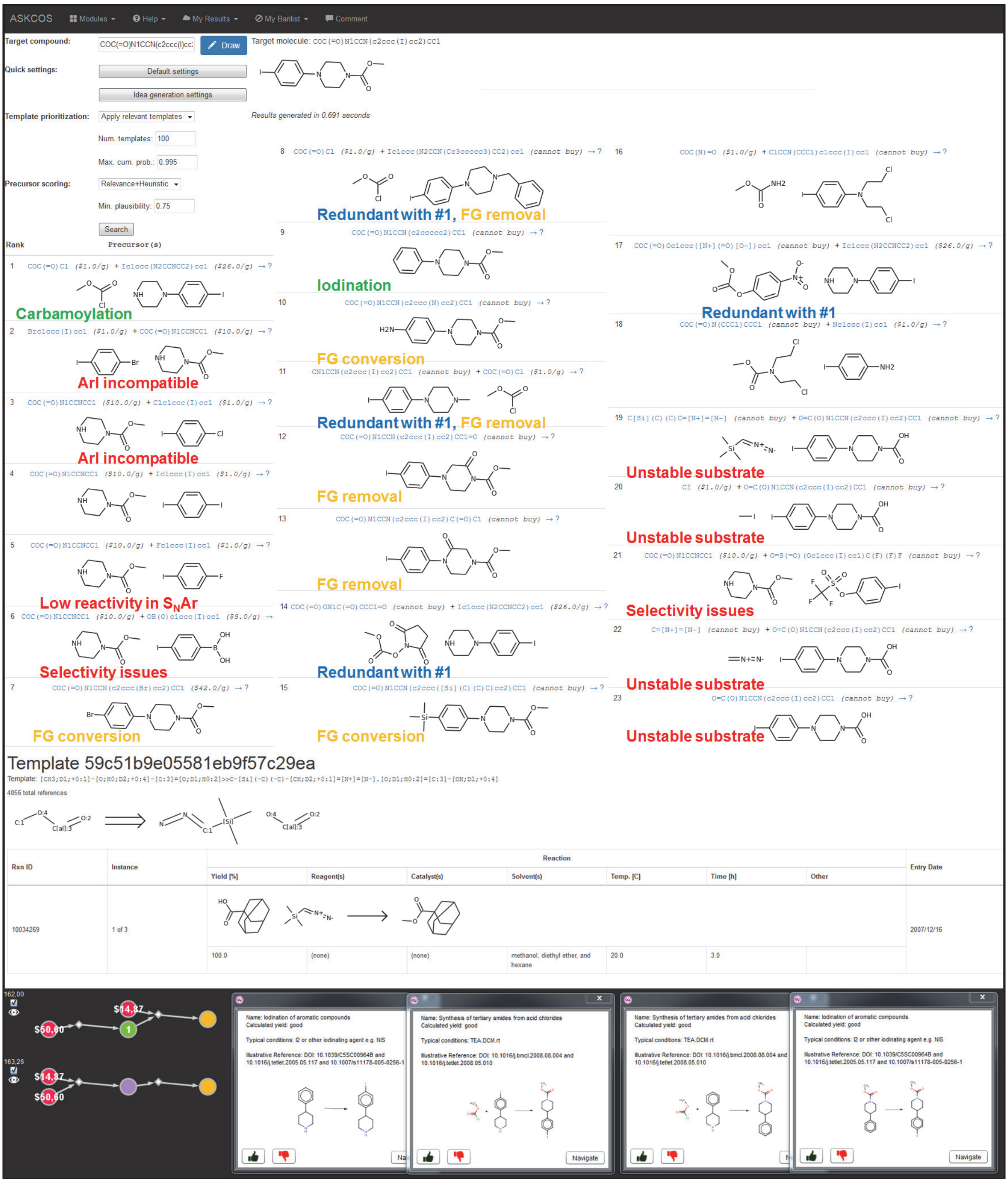
```
Rank    Precursor(s)
1   CO ($1.0/g) + O=C(O)C1CC2C=CC1C2 ($3.0/g) → ?
2   CI ($1.0/g) + O=C(O)C1CC2C=CC1C2 ($3.0/g) → ?
3   CO ($1.0/g) + O=C(Cl)C1CC2C=CC1C2 ($3.0/g) → ?
4   CO ($1.0/g) + O=CC1CC2C=CC1C2 ($2.0/g) → ?
5   CC(C)(C)OC(=O)C1CC2C=CC1C2 ($6.0/g) + CO ($1.0/g) → ?
6   COS(=O)(=O)OC ($12.0/g) + O=C(O)C1CC2C=CC1C2 ($3.0/g) → ?
7   COC(OC)OC ($1.0/g) + O=C(O)C1CC2C=CC1C2 ($3.0/g) → ?
8   CO ($1.0/g) + OCC1CC2C=CC1C2 ($5.0/g) → ?
9   COS(=O)(=O)C(F)(F)F ($3.0/g) + O=C(O)C1CC2C=CC1C2 ($3.0/g) → ?
10  C=[N+]=[N-] (cannot buy) + O=C(O)C1CC2C=CC1C2 ($3.0/g) → ?
11  O=C(O)C1CC2C=CC1C2 ($3.0/g) → ?
12  CO ($1.0/g) + N#CC1CC2C=CC1C2 ($7.0/g) → ?
13  C[Si](C)(C)C=[N+]=[N-] (cannot buy) + O=C(O)C1CC2C=CC1C2 ($3.0/g) → ?
14  N#CC1CC2C=CC1C2 ($7.0/g) → ?
15  C=[N+]=[N-] (cannot buy) + OCC1CC2C=CC1C2 ($5.0/g) → ?
16  C=[N+]=[N-] (cannot buy) + O=CC1CC2C=CC1C2 ($2.0/g) → ?
17  CI ($1.0/g) + O=C([O-])C1CC2C=CC1C2 (cannot buy) → ?
18  CCOC(=O)C1CC2C=CC1C2 (cannot buy) + CO ($1.0/g) → ?
19  C=C(OC)C1CC2C=CC1C2 (cannot buy) → ?
20  COC(=O)C1CC2CC1C=C2OS(=O)(=O)C(F)(F)F (cannot buy) → ?
21  COC(=O)C1CC2C=C(OS(=O)(=O)C(F)(F)F)C1C2 (cannot buy) → ?
22  COC(=O)C1CC2C=CC1C2OC(=S)n1ccnc1 (cannot buy) → ?
23  COC(=O)C1C2C=CC(C2)C1OC(=S)n1ccnc1 (cannot buy) → ?
```

Name: Diels-Alder
Calculated yield: good

Typical conditions: H2O.MeOH.EtOH.isooctane

Illustrative Reference: No Reference Found

Figure S4. Retrosynthetic planning of methyl bicyclo[2.2.1]hept-5-ene-2-carboxylate in MIT's ASKCOS system (http://askcos.mit.edu/retro/). As a reference, this compound can be prepared in *one* step from commercially available methyl acrylate and cyclopentadiene in the must-know, synthetically powerful Diels-Alder cycloaddition – this approach is easily found by Chematica (screenshot of Chematica's top-scoring solution shown at the bottom, on black background) but was not suggested by the neural network. Instead, several disconnections of the simple methyl ester (hydrolyses, transesterifications and modifications of oxidation states) dominated the top-20 results. Additionally, nonproductive removals of functional groups were suggested. All ASKCOS-proposed results for this target are shown.



Target compound: COC(=O)N1CCN(c2ccc(I)cc:

Target molecule: `COC(=O)N1CCN(c2ccc(I)cc2)CC1`

Quick settings:

Template prioritization: Apply relevant templates

Num. templates: 100

Max. cum. prob.: 0.995

Precursor scoring: Relevance+Heuristic

Min. plausibility: 0.75

Results generated in 0.691 seconds

Rank	Precursor(s)
1	`COC(=O)Cl` *($1.0/g)* + `Ic1ccc(N2CCNCC2)cc1` *($26.0/g)* → ?
2	`Brc1ccc(I)cc1` *($1.0/g)* + `COC(=O)N1CCNCC1` *($10.0/g)* → ?
3	`COC(=O)N1CCNCC1` *($10.0/g)* + `Clc1ccc(I)cc1` *($1.0/g)* → ?
4	`COC(=O)N1CCNCC1` *($10.0/g)* + `Ic1ccc(I)cc1` *($1.0/g)* → ?
5	`COC(=O)N1CCNCC1` *($10.0/g)* + `Fc1ccc(I)cc1` *($1.0/g)* → ?
6	`COC(=O)N1CCNCC1` *($10.0/g)* + `OB(O)c1ccc(I)cc1` *($9.0/g)* →
7	`COC(=O)N1CCN(c2ccc(Br)cc2)CC1` *($42.0/g)* → ?
8	`COC(=O)Cl` *($1.0/g)* + `Ic1ccc(N2CCN(Cc3ccccc3)CC2)cc1` *(cannot buy)* → ?
9	`COC(=O)N1CCN(c2ccccc2)CC1` *(cannot buy)* → ?
10	`COC(=O)N1CCN(c2ccc(N)cc2)CC1` *(cannot buy)* → ?
11	`CN1CCN(c2ccc(I)cc2)CC1` *(cannot buy)* + `COC(=O)Cl` *($1.0/g)* → ?
12	`COC(=O)N1CCN(c2ccc(I)cc2)CC1=O` *(cannot buy)* → ?
13	`COC(=O)N1CCN(c2ccc(I)cc2)C(=O)C1` *(cannot buy)* → ?
14	`COC(=O)ON1C(=O)CCC1=O` *(cannot buy)* + `Ic1ccc(N2CCNCC2)cc1` *($26.0/g)* → ?
15	`COC(=O)N1CCN(c2ccc([Si](C)(C)C)cc2)CC1` *(cannot buy)* → ?
16	`COC(N)=O` *($1.0/g)* + `ClCCN(CCCl)c1ccc(I)cc1` *(cannot buy)* → ?
17	`COC(=O)Oc1ccc([N+](=O)[O-])cc1` *(cannot buy)* + `Ic1ccc(N2CCNCC2)cc1` *($26.0/g)* → ?
18	`COC(=O)N(CCCl)CCCl` *(cannot buy)* + `Nc1ccc(I)cc1` *($1.0/g)* → ?
19	`C[Si](C)(C)C=[N+]=[N-]` *(cannot buy)* + `O=C(O)N1CCN(c2ccc(I)cc2)CC1` *(cannot buy)* → ?
20	`CI` *($1.0/g)* + `O=C(O)N1CCN(c2ccc(I)cc2)CC1` *(cannot buy)* → ?
21	`COC(=O)N1CCNCC1` *($10.0/g)* + `O=S(=O)(Oc1ccc(I)cc1)C(F)(F)F` *(cannot buy)* → ?
22	`C=[N+]=[N-]` *(cannot buy)* + `O=C(O)N1CCN(c2ccc(I)cc2)CC1` *(cannot buy)* → ?
23	`O=C(O)N1CCN(c2ccc(I)cc2)CC1` *(cannot buy)* → ?

Template 59c51b9e05581eb9f57c29ea

Template: `[CH3;D1;+0:1]-[O;H0;D2;+0:4]-[C:3]=[O;D1;H0:2]>>C-[Si](-C)(-C)-[CH;D2;+0:1]=[N+]=[N-].[O;D1;H0:2]=[C:3]-[OH;D1;+0:4]`

4056 total references

Rxn ID	Instance	Reaction							Entry Date
		Yield [%]	Reagent(s)	Catalyst(s)	Solvent(s)	Temp. [C]	Time [h]	Other	
10034269	1 of 3	100.0	(none)	(none)	methanol, diethyl ether, and hexane	20.0	3.0		2007/12/16

Name: Iodination of aromatic compounds
Calculated yield: good

Typical conditions: I2 or other iodinating agent e.g. NIS

Illustrative Reference: DOI: 10.1039/C5SC00964B and 10.1016/j.tetlet.2005.05.117 and 10.1007/s11178-005-0256-1

Name: Synthesis of tertiary amides from acid chlorides
Calculated yield: good

Typical conditions: TEA.DCM.rt

Illustrative Reference: DOI: 10.1016/j.bmcl.2008.08.004 and 10.1016/j.tetlet.2008.05.010

Name: Synthesis of tertiary amides from acid chlorides
Calculated yield: good

Typical conditions: TEA.DCM.rt

Illustrative Reference: DOI: 10.1016/j.bmcl.2008.08.004 and 10.1016/j.tetlet.2008.05.010

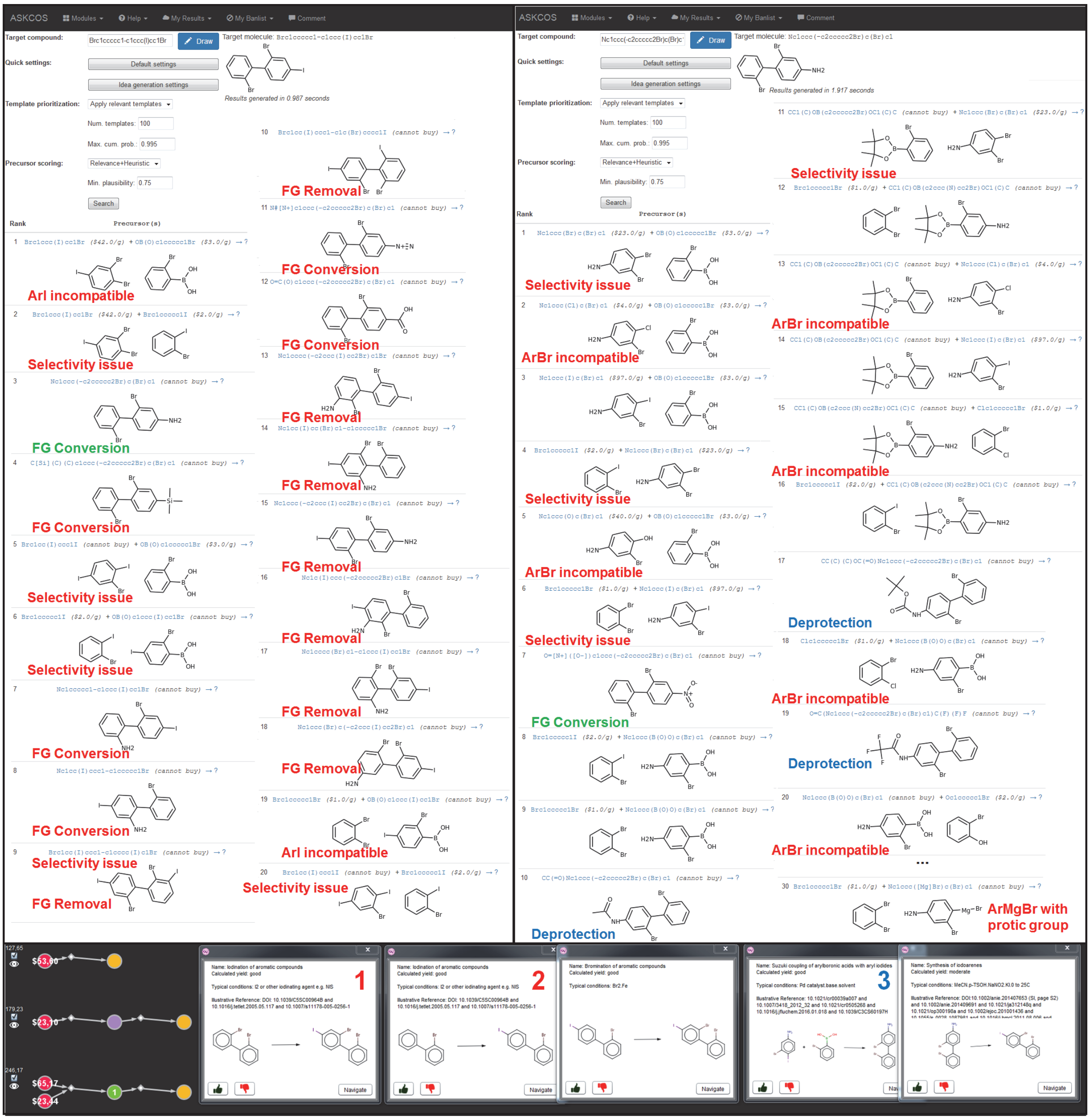
Name: Iodination of aromatic compounds
Calculated yield: good

Typical conditions: I2 or other iodinating agent e.g. NIS

Illustrative Reference: DOI: 10.1039/C5SC00964B and 10.1016/j.tetlet.2005.05.117 and 10.1007/s11178-005-0256-1

Figure S5. Retrosynthetic planning of methyl 4-(4-iodo-phenyl) piperazine-1-carboxylate in MIT's ASKCOS system. As a reference, the synthesis of this class of compounds is usually finalized by the formation of carbamate or electrophilic aromatic iodination – this approaches are easily found by Chematica (screenshots of the top-scoring solutions at the bottom). Although the formation of carbamate was the top ASKCOS'prediction, the electrophilic aromatic iodination was only its ninth suggestion. In addition, several other suggestions from top20 results raise reactivity concerns. For instance, Buchwald-type amination of an aryl chloride or bromide (reactions ranked #2 and #3) is virtually impossible in the presence of a more reactive aryl iodide (see main text, Figure 6).

Analogous reaction of an aryl fluoride ranked as #5 (occurring via S_NAr mechanism) has marginal chances to succeed due to lack of electron withdrawing groups activating the ring towards the nucleophilic substitution. Additionally, reactions #6 and #21 raise chemoselectivity concerns due to the presence of an aryl iodide. Moreover, ASKCOS proposed (#19,#20,#22,#23) unstable and decarboxylation-prone carbamic acid as a substrate. Inspection of the reaction template responsible for the outcome shown in #19 clearly demonstrates that automatically generated reaction rule cannot distinguish groups (here, unstable carbamic and stable carboxylic acids) of quite different reactivities. All returned results are shown.



Target compound: Brc1ccccc1-c1ccc(I)cc1Br

Target molecule: Brc1ccccc1-c1ccc(I)cc1Br

Results generated in 0.987 seconds

Template prioritization: Apply relevant templates

Num. templates: 100

Max. cum. prob.: 0.995

Precursor scoring: Relevance+Heuristic

Min. plausibility: 0.75

Rank Precursor(s)

1 Brc1ccc(I)cc1Br ($42.0/g) + OB(O)c1ccccc1Br ($3.0/g) → ?

2 Brc1ccc(I)cc1Br ($42.0/g) + Brc1ccccc1I ($2.0/g) → ?

3 Nc1ccc(-c2ccccc2Br)c(Br)c1 (cannot buy) → ?

4 C[Si](C)(C)c1ccc(-c2ccccc2Br)c(Br)c1 (cannot buy) → ?

5 Brc1cc(I)ccc1I (cannot buy) + OB(O)c1ccccc1Br ($3.0/g) → ?

6 Brc1ccccc1I ($2.0/g) + OB(O)c1ccc(I)cc1Br (cannot buy) → ?

7 Nc1ccccc1-c1ccc(I)cc1Br (cannot buy) → ?

8 Nc1cc(I)ccc1-c1ccccc1Br (cannot buy) → ?

9 Brc1cc(I)ccc1-c1cccc(I)c1Br (cannot buy) → ?

10 Brc1cc(I)ccc1-c1c(Br)cccc1I (cannot buy) → ?

11 N#[N+]c1ccc(-c2ccccc2Br)c(Br)c1 (cannot buy) → ?

12 O=C(O)c1ccc(-c2ccccc2Br)c(Br)c1 (cannot buy) → ?

13 Nc1cccc(-c2ccc(I)cc2Br)c1Br (cannot buy) → ?

14 Nc1cc(I)cc(Br)c1-c1ccccc1Br (cannot buy) → ?

15 Nc1ccc(-c2ccc(I)cc2Br)c(Br)c1 (cannot buy) → ?

16 Nc1c(I)ccc(-c2ccccc2Br)c1Br (cannot buy) → ?

17 Nc1cccc(Br)c1-c1ccc(I)cc1Br (cannot buy) → ?

18 Nc1ccc(Br)c(-c2ccc(I)cc2Br)c1 (cannot buy) → ?

19 Brc1ccccc1Br ($1.0/g) + OB(O)c1ccc(I)cc1Br (cannot buy) → ?

20 Brc1cc(I)ccc1I (cannot buy) + Brc1ccccc1I ($2.0/g) → ?

Target compound: Nc1ccc(-c2ccccc2Br)c(Br)c

Target molecule: Nc1ccc(-c2ccccc2Br)c(Br)c1

Results generated in 1.917 seconds

Template prioritization: Apply relevant templates

Num. templates: 100

Max. cum. prob.: 0.995

Precursor scoring: Relevance+Heuristic

Min. plausibility: 0.75

Rank Precursor(s)

1 Nc1ccc(Br)c(Br)c1 ($23.0/g) + OB(O)c1ccccc1Br ($3.0/g) → ?

2 Nc1ccc(Cl)c(Br)c1 ($4.0/g) + OB(O)c1ccccc1Br ($3.0/g) → ?

3 Nc1ccc(I)c(Br)c1 ($97.0/g) + OB(O)c1ccccc1Br ($3.0/g) → ?

4 Brc1ccccc1I ($2.0/g) + Nc1ccc(Br)c(Br)c1 ($23.0/g) → ?

5 Nc1ccc(O)c(Br)c1 ($40.0/g) + OB(O)c1ccccc1Br ($3.0/g) → ?

6 Brc1ccccc1Br ($1.0/g) + Nc1ccc(I)c(Br)c1 ($97.0/g) → ?

7 O=[N+]([O-])c1ccc(-c2ccccc2Br)c(Br)c1 (cannot buy) → ?

8 Brc1ccccc1I ($2.0/g) + Nc1ccc(B(O)O)c(Br)c1 (cannot buy) → ?

9 Brc1ccccc1Br ($1.0/g) + Nc1ccc(B(O)O)c(Br)c1 (cannot buy) → ?

10 CC(=O)Nc1ccc(-c2ccccc2Br)c(Br)c1 (cannot buy) → ?

11 CC1(C)OB(c2ccccc2Br)OC1(C)C (cannot buy) + Nc1ccc(Br)c(Br)c1 ($23.0/g) → ?

12 Brc1ccccc1Br ($1.0/g) + CC1(C)OB(c2ccc(N)cc2Br)OC1(C)C (cannot buy) → ?

13 CC1(C)OB(c2ccccc2Br)OC1(C)C (cannot buy) + Nc1ccc(Cl)c(Br)c1 ($4.0/g) → ?

14 CC1(C)OB(c2ccccc2Br)OC1(C)C (cannot buy) + Nc1ccc(I)c(Br)c1 ($97.0/g) → ?

15 CC1(C)OB(c2ccc(N)cc2Br)OC1(C)C (cannot buy) + Clc1ccccc1Br ($1.0/g) → ?

16 Brc1ccccc1I ($2.0/g) + CC1(C)OB(c2ccc(N)cc2Br)OC1(C)C (cannot buy) → ?

17 CC(C)(C)OC(=O)Nc1ccc(-c2ccccc2Br)c(Br)c1 (cannot buy) → ?

18 Clc1ccccc1Br ($1.0/g) + Nc1ccc(B(O)O)c(Br)c1 (cannot buy) → ?

19 O=C(Nc1ccc(-c2ccccc2Br)c(Br)c1)C(F)(F)F (cannot buy) → ?

20 Nc1ccc(B(O)O)c(Br)c1 (cannot buy) + Oc1ccccc1Br ($2.0/g) → ?

...

30 Brc1ccccc1Br ($1.0/g) + Nc1ccc([Mg]Br)c(Br)c1 (cannot buy) → ?

Name: Iodination of aromatic compounds
Calculated yield: good
Typical conditions: I2 or other iodinating agent e.g. NIS
Illustrative Reference: DOI: 10.1039/C5SC00964B and 10.1016/j.tetlet.2005.05.117 and 10.1007/s11178-005-0256-1

Name: Iodination of aromatic compounds
Calculated yield: good
Typical conditions: I2 or other iodinating agent e.g. NIS
Illustrative Reference: DOI: 10.1039/C5SC00964B and 10.1016/j.tetlet.2005.05.117 and 10.1007/s11178-005-0256-1

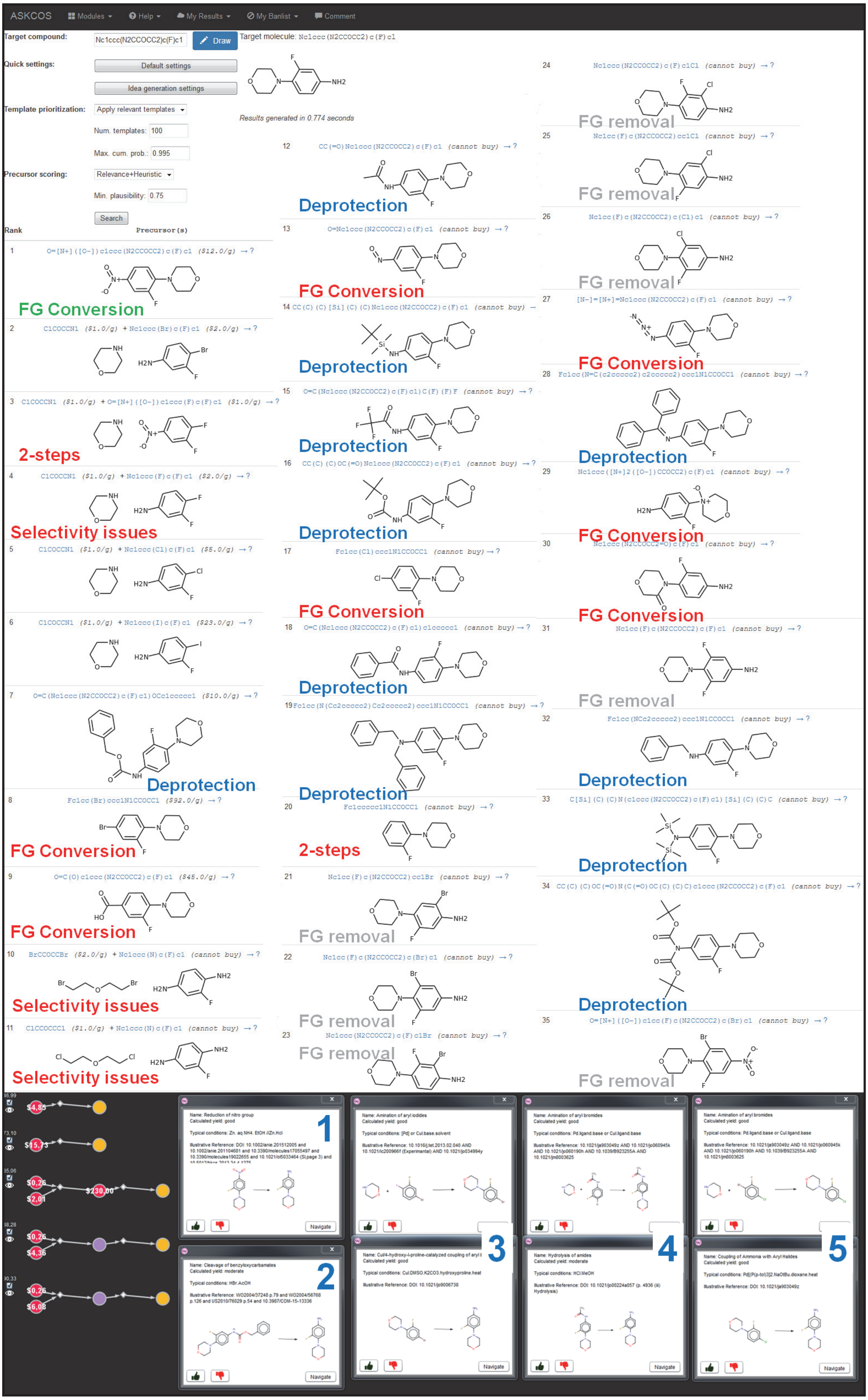
Name: Bromination of aromatic compounds
Calculated yield: good
Typical conditions: Br2.Fe

Name: Suzuki coupling of arylboronic acids with aryl iodides
Calculated yield: good
Typical conditions: Pd catalyst.base.solvent
Illustrative Reference: 10.1021/cr00039a007 and 10.1007/3418_2012_32 and 10.1021/cr0505268 and 10.1016/j.jfluchem.2016.01.018 and 10.1039/C3CS60197H

Name: Synthesis of iodoarenes
Calculated yield: moderate
Typical conditions: MeCN.p-TSOH.NaNO2.KI.0 to 25C
Illustrative Reference: DOI:10.1002/anie.201407653 (SI, page S2) and 10.1002/anie.201409691 and 10.1021/ja312148q and 10.1021/op300198a and 10.1002/ejoc.201001436 and

Figure S6. Attempted multistep retrosynthetic planning of 2,2'-dibromo-iodobiphenyl. This class of polyhalogenated building blocks is usually prepared via iodination, Suzuki coupling, and Sandmeyer reaction. ASKCOS suggestions for this compound rise several serious selectivity and cross-reactivity concerns. For example, Suzuki coupling (#1, #19) with aryl bromide will not proceed if a more reactive aryl iodide is present (see main text, Figure 6). Additionally, an aryl halide cross coupling shown in (#2, #20), Suzuki coupling (#5,#6), and selective removal of one of the iodides (#9 and #10) will lead to a mixture of products (due to a presence of multiple nonequivalent groups). As in previous examples, multiple FG removals (here: deaminations) were also present in top20 results. Expanding one of the proposed intermediates – a substrate for Sandmeyer reaction – leads to the set of second-step suggestions (right panel) often suffering from the abovementioned selectivity and reactivity concerns: arylation of an aryl chloride

(#2,#13,#15) or phenol (#5,#20) is proposed in the presence of an incompatible aryl bromide while cross coupling of aryl halides (#4) or Suzuki coupling with dibromoaniline (#1,#11) will lead to a mixture of products. Finally, in #30 arylmagnesium reagent with protic NH_2 group is used as a substrate while these functional groups simply cannot exist together. Left panel: top 20 out of 28 returned results are shown, right panel: top 20 and #30 out of 41 returned results are shown. Full synthetic pathways generated autonomously by Chematica (top 3 shown in the bottom part) rely either on the electrophilic aromatic halogenations (#1, #2) or take advantage of Suzuki coupling and Sandmeyer reaction (#3). This is one example we found where some of Chematica's suggestions raise concerns: namely aromatic substitutions of substrates suggested in #1 and the second step of #2 are known to yield mainly regioisomeric products (here: 2,2'-dibromo-5-iodobiphenyl and 2,5-dibromo-4'-iodobiphenyl). This inaccuracy is due to the Hammett/Hueckel/Proton-affinity based filter evaluating aromatic substitutions (90% correct, the example here is obviously in the 10% of erroneous predictions). However, the third solution returned by Chematica does not rise any reactivity and selectivity concerns.



Target compound: Nc1ccc(N2CCOCC2)c(F)c1

Target molecule: `Nc1ccc(N2CCOCC2)c(F)c1`

Quick settings:

Template prioritization: Apply relevant templates

Num. templates: 100

Max. cum. prob.: 0.995

Precursor scoring: Relevance+Heuristic

Min. plausibility: 0.75

Results generated in 0.774 seconds

Rank	Precursor(s)
1	`O=[N+]([O-])c1ccc(N2CCOCC2)c(F)c1` *($12.0/g)* → ? FG Conversion
2	`C1COCCN1` *($1.0/g)* + `Nc1ccc(Br)c(F)c1` *($2.0/g)* → ?
3	`C1COCCN1` *($1.0/g)* + `O=[N+]([O-])c1ccc(F)c(F)c1` *($1.0/g)* → ? 2-steps
4	`C1COCCN1` *($1.0/g)* + `Nc1ccc(F)c(F)c1` *($2.0/g)* → ? Selectivity issues
5	`C1COCCN1` *($1.0/g)* + `Nc1ccc(Cl)c(F)c1` *($5.0/g)* → ?
6	`C1COCCN1` *($1.0/g)* + `Nc1ccc(I)c(F)c1` *($23.0/g)* → ?
7	`O=C(Nc1ccc(N2CCOCC2)c(F)c1)OCc1ccccc1` *($10.0/g)* → ? Deprotection
8	`Fc1cc(Br)ccc1N1CCOCC1` *($92.0/g)* → ? FG Conversion
9	`O=C(O)c1ccc(N2CCOCC2)c(F)c1` *($45.0/g)* → ? FG Conversion
10	`BrCCOCCBr` *($2.0/g)* + `Nc1ccc(N)c(F)c1` *(cannot buy)* → ? Selectivity issues
11	`ClCCOCCCl` *($1.0/g)* + `Nc1ccc(N)c(F)c1` *(cannot buy)* → ? Selectivity issues
12	`CC(=O)Nc1ccc(N2CCOCC2)c(F)c1` *(cannot buy)* → ? Deprotection
13	`O=Nc1ccc(N2CCOCC2)c(F)c1` *(cannot buy)* → ? FG Conversion
14	`CC(C)(C)[Si](C)(C)Nc1ccc(N2CCOCC2)c(F)c1` *(cannot buy)* → Deprotection
15	`O=C(Nc1ccc(N2CCOCC2)c(F)c1)C(F)(F)F` *(cannot buy)* → ? Deprotection
16	`CC(C)(C)OC(=O)Nc1ccc(N2CCOCC2)c(F)c1` *(cannot buy)* → ? Deprotection
17	`Fc1cc(Cl)ccc1N1CCOCC1` *(cannot buy)* → ? FG Conversion
18	`O=C(Nc1ccc(N2CCOCC2)c(F)c1)c1ccccc1` *(cannot buy)* → ? Deprotection
19	`Fc1cc(N(Cc2ccccc2)Cc2ccccc2)ccc1N1CCOCC1` *(cannot buy)* → ? Deprotection
20	`Fc1ccccc1N1CCOCC1` *(cannot buy)* → ? 2-steps
21	`Nc1cc(F)c(N2CCOCC2)cc1Br` *(cannot buy)* → ? FG removal
22	`Nc1cc(F)c(N2CCOCC2)c(Br)c1` *(cannot buy)* → ? FG removal
23	`Nc1ccc(N2CCOCC2)c(F)c1Br` *(cannot buy)* → ? FG removal
24	`Nc1ccc(N2CCOCC2)c(F)c1Cl` *(cannot buy)* → ? FG removal
25	`Nc1cc(F)c(N2CCOCC2)cc1Cl` *(cannot buy)* → ? FG removal
26	`Nc1cc(F)c(N2CCOCC2)c(Cl)c1` *(cannot buy)* → ? FG removal
27	`[N-]=[N+]=Nc1ccc(N2CCOCC2)c(F)c1` *(cannot buy)* → ? FG Conversion
28	`Fc1cc(N=C(c2ccccc2)c2ccccc2)ccc1N1CCOCC1` *(cannot buy)* → ? Deprotection
29	`Nc1ccc([N+]2([O-])CCOCC2)c(F)c1` *(cannot buy)* → ? FG Conversion
30	`Nc1ccc(N2CCOCC2=O)c(F)c1` *(cannot buy)* → ? FG Conversion
31	`Nc1cc(F)c(N2CCOCC2)c(F)c1` *(cannot buy)* → ? FG removal
32	`Fc1cc(NCc2ccccc2)ccc1N1CCOCC1` *(cannot buy)* → ? Deprotection
33	`C[Si](C)(C)N(c1ccc(N2CCOCC2)c(F)c1)[Si](C)(C)C` *(cannot buy)* → ? Deprotection
34	`CC(C)(C)OC(=O)N(C(=O)OC(C)(C)C)c1ccc(N2CCOCC2)c(F)c1` *(cannot buy)* → ? Deprotection
35	`O=[N+]([O-])c1cc(F)c(N2CCOCC2)c(Br)c1` *(cannot buy)* → ? FG removal

1

Name: Reduction of nitro group
Calculated yield: good

Typical conditions: Zn. aq NH4. EtOH //Zn.Hcl

Illustrative Reference: DOI: 10.1002/anie.201512005 and 10.1002/anie.201104681 and 10.3390/molecules17055497 and 10.3390/molecules19022655 and 10.1021/ol5033464 (SI,page 3) and

2

Name: Cleavage of benzyloxycarbamates
Calculated yield: moderate

Typical conditions: HBr.AcOH

Illustrative Reference: WO2004/37248 p.79 and WO2004/56768 p.126 and US2010/76029 p.54 and 10.3987/COM-15-13336

Name: Amination of aryl iodides
Calculated yield: good

Typical conditions: [Pd] or CuI.base.solvent

Illustrative Reference: 10.1016/j.tet.2013.02.040 AND 10.1021/ic200966f (Experimantal) AND 10.1021/jo034994y

3

Name: CuI/4-hydroxy-l-proline-catalyzed coupling of aryl b
Calculated yield: good

Typical conditions: CuI.DMSO.K2CO3.hydroxyproline.heat

Illustrative Reference: DOI: 10.1021/jo9006738

Name: Amination of aryl bromides
Calculated yield: good

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

Illustrative Reference: 10.1021/ja903049z AND 10.1021/jo060945k AND 10.1021/jo060190h AND 10.1039/B923255A AND 10.1021/jm8003625

4

Name: Hydrolysis of amides
Calculated yield: moderate

Typical conditions: HCl.MeOH

Illustrative Reference: DOI: 10.1021/jo00224a057 (p. 4936 (iii) Hydrolysis)

Name: Amination of aryl bromides
Calculated yield: good

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

Illustrative Reference: 10.1021/ja903049z AND 10.1021/jo060945k AND 10.1021/jo060190h AND 10.1039/B923255A AND 10.1021/jm8003625

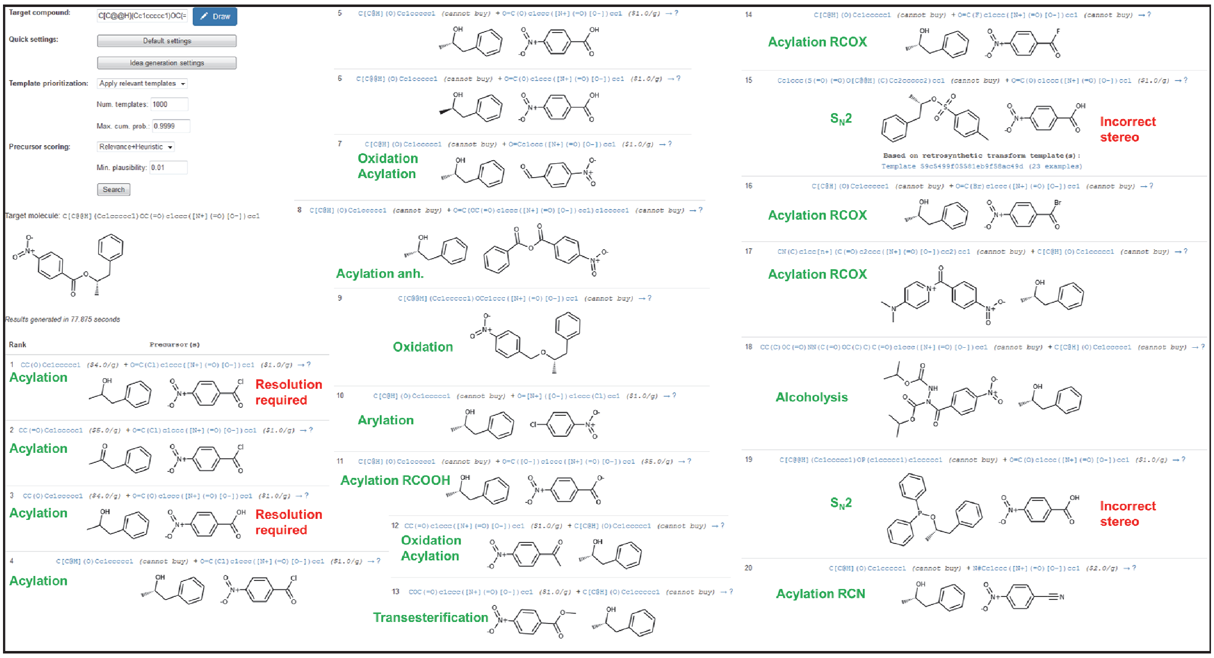
5

Name: Coupling of Ammonia with Aryl Halides
Calculated yield: good

Typical conditions: Pd[(P(p-tol)3]2.NaOtBu.dioxane.heat

Illustrative Reference: DOI: 10.1021/ja903049z

Figure S7. Retrosynthetic planning of Linezolid's intermediate in MIT's ASKCOS system. The target is of interest since it is found in many patented routes we describe in [69]. Several of ASKCOS' suggestions for this target rise serious concerns of low selectivity and/or insufficient chemical reactivity. Selective functionalization of unsymmetrical diamine (#10,#11) has never been reported and will deliver a mixture of products. Presence of the electron-donating amine group in #4 deactivating the ring towards S_NAr reaction is highly problematic and renders this transformation unfeasible to perform – even more reactive 3,4,5-trifluoroaniline required heating to 180 °C for 36 h in neat morpholine to give the product in moderate yield (*Eur. J. Org. Chem.* **2012**, 7048–7052). Selective substitution of difluoroaniline (#4) is also a currently an unknown process – in fact, the attempted reaction with alcohol (*Eur. J. Org. Chem.* **2012**, 7048–7052) led to a 1:1 mixture of products. As in previous examples, several (19/35) unproductive removals of protecting groups (blue) or halogen atoms (grey) were present in top35 results. Additionally, #3 (substitution/reduction) and #20 (nitration/reduction) are overlapping with the top prediction. Top 35 out of 39 returned results are shown. In contrast, synthetic pathways returned by Chematica (bottom) do not suffer from any chemical reactivity issues.



Target compound: C[C@@H](Cc1ccccc1)OC(=

Quick settings:

Template prioritization: Apply relevant templates

Num. templates: 1000

Max. cum. prob.: 0.9999

Precursor scoring: Relevance+Heuristic

Min. plausibility: 0.01

Target molecule: C[C@@H](Cc1ccccc1)OC(=O)c1ccc([N+](=O)[O-])cc1

Results generated in 77.875 seconds

Rank Precursor(s)

1 CC(O)Cc1ccccc1 *($4.0/g)* + O=C(Cl)c1ccc([N+](=O)[O-])cc1 *($1.0/g)* → ?

2 CC(=O)Cc1ccccc1 *($5.0/g)* + O=C(Cl)c1ccc([N+](=O)[O-])cc1 *($1.0/g)* → ?

3 CC(O)Cc1ccccc1 *($4.0/g)* + O=C(O)c1ccc([N+](=O)[O-])cc1 *($1.0/g)* → ?

4 C[C@H](O)Cc1ccccc1 *(cannot buy)* + O=C(Cl)c1ccc([N+](=O)[O-])cc1 *($1.0/g)* → ?

5 C[C@H](O)Cc1ccccc1 *(cannot buy)* + O=C(O)c1ccc([N+](=O)[O-])cc1 *($1.0/g)* → ?

6 C[C@@H](O)Cc1ccccc1 *(cannot buy)* + O=C(O)c1ccc([N+](=O)[O-])cc1 *($1.0/g)* → ?

7 C[C@H](O)Cc1ccccc1 *(cannot buy)* + O=Cc1ccc([N+](=O)[O-])cc1 *($1.0/g)* → ?

8 C[C@H](O)Cc1ccccc1 *(cannot buy)* + O=C(OC(=O)c1ccc([N+](=O)[O-])cc1)c1ccccc1 *(cannot buy)* → ?

9 C[C@@H](Cc1ccccc1)OCc1ccc([N+](=O)[O-])cc1 *(cannot buy)* → ?

10 C[C@H](O)Cc1ccccc1 *(cannot buy)* + O=[N+]([O-])c1ccc(Cl)cc1 *($1.0/g)* → ?

11 C[C@H](O)Cc1ccccc1 *(cannot buy)* + O=C([O-])c1ccc([N+](=O)[O-])cc1 *($5.0/g)* → ?

12 CC(=O)c1ccc([N+](=O)[O-])cc1 *($1.0/g)* + C[C@H](O)Cc1ccccc1 *(cannot buy)* → ?

13 COC(=O)c1ccc([N+](=O)[O-])cc1 *($1.0/g)* + C[C@H](O)Cc1ccccc1 *(cannot buy)* → ?

14 C[C@H](O)Cc1ccccc1 *(cannot buy)* + O=C(F)c1ccc([N+](=O)[O-])cc1 *(cannot buy)* → ?

15 Cc1ccc(S(=O)(=O)O[C@@H](C)Cc2ccccc2)cc1 *(cannot buy)* + O=C(O)c1ccc([N+](=O)[O-])cc1 *($1.0/g)* → ?

Based on retrosynthetic transform template(s):
Template 59c5499f05581eb9f58ac49d (23 examples)

16 C[C@H](O)Cc1ccccc1 *(cannot buy)* + O=C(Br)c1ccc([N+](=O)[O-])cc1 *(cannot buy)* → ?

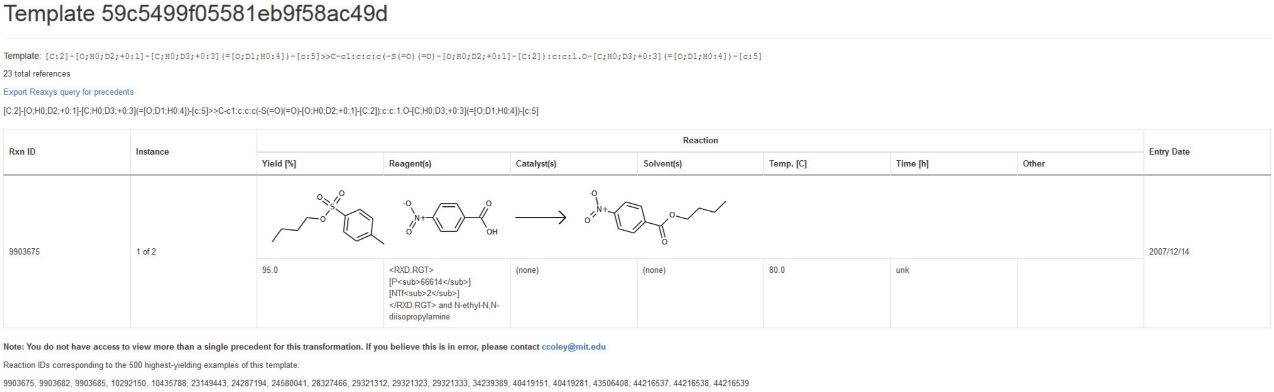
17 CN(C)c1cc[n+](C(=O)c2ccc([N+](=O)[O-])cc2)cc1 *(cannot buy)* + C[C@H](O)Cc1ccccc1 *(cannot buy)* → ?

18 CC(C)OC(=O)NN(C(=O)OC(C)C)C(=O)c1ccc([N+](=O)[O-])cc1 *(cannot buy)* + C[C@H](O)Cc1ccccc1 *(cannot buy)* → ?

19 C[C@@H](Cc1ccccc1)OP(c1ccccc1)c1ccccc1 *(cannot buy)* + O=C(O)c1ccc([N+](=O)[O-])cc1 *($1.0/g)* → ?

20 C[C@H](O)Cc1ccccc1 *(cannot buy)* + N#Cc1ccc([N+](=O)[O-])cc1 *($2.0/g)* → ?

Figure S8. Retrosynthetic planning of a chiral acylated alcohol in the ASKCOS system. Displacement of mesylate (#15) or alkoxydiphenylphosphine (#19) with carboxylic acid occurs with inversion of configuration via S_N2 mechanism. However, the reaction templates for these reactions generate substrates corresponding to a chemically incorrect stereoretentive process. See **Figure S9** for details of ASKCOS' template for #15.



Template 59c5499f05581eb9f58ac49d

Template: `[C:2]-[O;H0;D2;+0:1]-[C;H0;D3;+0:3](=[O;D1;H0:4])-[c:5]>>C-c1:c:c:c(-S(=O)(=O)-[O;H0;D2;+0:1]-[C:2]):c:c:1.O-[C;H0;D3;+0:3](=[O;D1;H0:4])-[c:5]`

23 total references

Export Reaxys query for precedents

[C:2]-[O;H0;D2;+0:1]-[C;H0;D3;+0:3](=[O;D1;H0:4])-[c:5]>>C-c1:c:c:c(-S(=O)(=O)-[O;H0;D2;+0:1]-[C:2]):c:c:1.O-[C;H0;D3;+0:3](=[O;D1;H0:4])-[c:5]

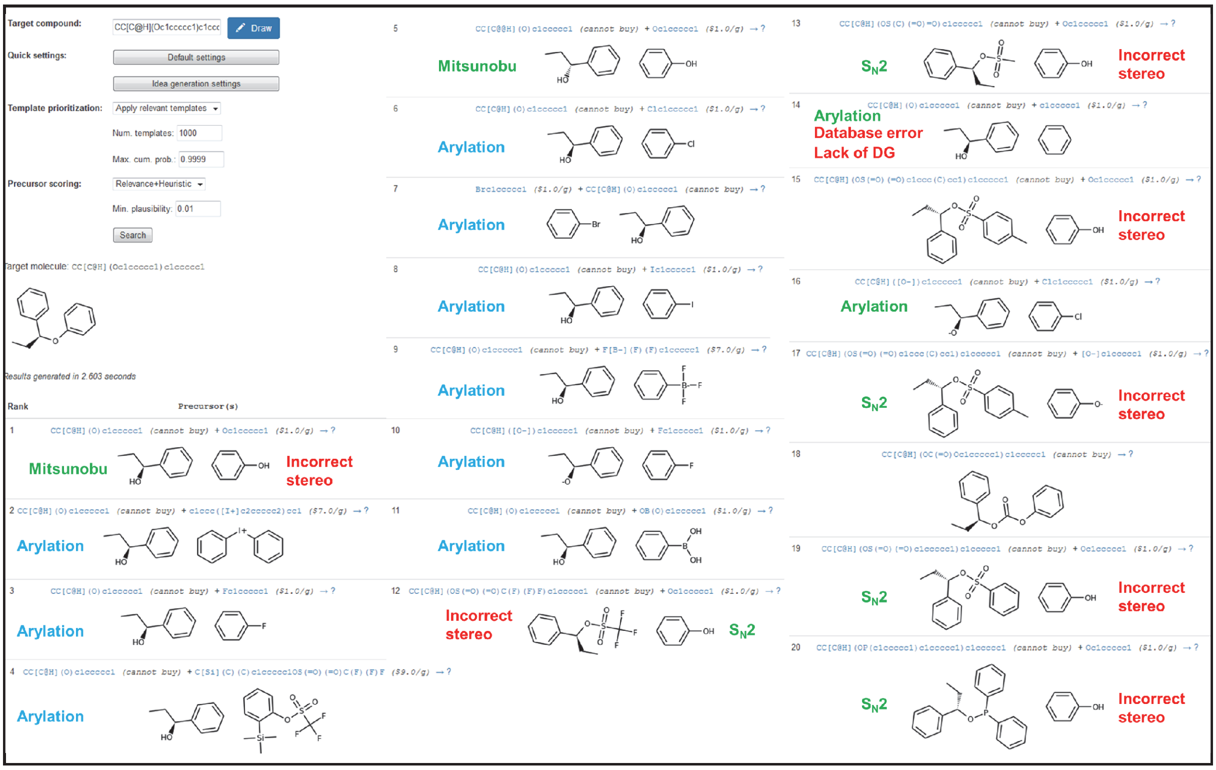
Rxn ID	Instance	Reaction							Entry Date
		Yield [%]	Reagent(s)	Catalyst(s)	Solvent(s)	Temp. [C]	Time [h]	Other	
9903675	1 of 2	95.0	<RXD.RGT> [P₆₆₆₁₄] [NTf₂] </RXD.RGT> and N-ethyl-N,N-diisopropylamine	(none)	(none)	80.0	unk		2007/12/14

Note: You do not have access to view more than a single precedent for this transformation. If you believe this is in error, please contact ccoley@mit.edu

Reaction IDs corresponding to the 500 highest-yielding examples of this template:

9903675, 9903682, 9903685, 10292150, 10435788, 23149443, 24287194, 24580041, 28327466, 29321312, 29321323, 29321333, 34239389, 40419151, 40419281, 43506408, 44216537, 44216538, 44216539

Figure S9. Automatically extracted core for the substitution of a mesylate with a carboxylic acid ignores inversion of configuration and generates substrates with improper stereochemistry. The same template is not limited to primary and secondary mesylates and allows for substrates bearing hardly reactive, tertiary mesylates.



Target compound: CC[C@H](Oc1ccccc1)c1ccc

Quick settings: Default settings / Idea generation settings

Template prioritization: Apply relevant templates

Num. templates: 1000

Max. cum. prob.: 0.9999

Precursor scoring: Relevance+Heuristic

Min. plausibility: 0.01

Target molecule: CC[C@H](Oc1ccccc1)c1ccccc1

Results generated in 2.603 seconds

Rank Precursor(s)

1 CC[C@H](O)c1ccccc1 (cannot buy) + Oc1ccccc1 ($1.0/g) → ?

2 CC[C@H](O)c1ccccc1 (cannot buy) + c1ccc([I+]c2ccccc2)cc1 ($7.0/g) → ?

3 CC[C@H](O)c1ccccc1 (cannot buy) + Fc1ccccc1 ($1.0/g) → ?

4 CC[C@H](O)c1ccccc1 (cannot buy) + C[Si](C)(C)c1ccccc1OS(=O)(=O)C(F)(F)F ($9.0/g) → ?

5 CC[C@@H](O)c1ccccc1 (cannot buy) + Oc1ccccc1 ($1.0/g) → ?

6 CC[C@H](O)c1ccccc1 (cannot buy) + Clc1ccccc1 ($1.0/g) → ?

7 Brc1ccccc1 ($1.0/g) + CC[C@H](O)c1ccccc1 (cannot buy) → ?

8 CC[C@H](O)c1ccccc1 (cannot buy) + Ic1ccccc1 ($1.0/g) → ?

9 CC[C@H](O)c1ccccc1 (cannot buy) + F[B-](F)(F)c1ccccc1 ($7.0/g) → ?

10 CC[C@H]([O-])c1ccccc1 (cannot buy) + Fc1ccccc1 ($1.0/g) → ?

11 CC[C@H](O)c1ccccc1 (cannot buy) + OB(O)c1ccccc1 ($1.0/g) → ?

12 CC[C@H](OS(=O)(=O)C(F)(F)F)c1ccccc1 (cannot buy) + Oc1ccccc1 ($1.0/g) → ?

13 CC[C@H](OS(C)(=O)=O)c1ccccc1 (cannot buy) + Oc1ccccc1 ($1.0/g) → ?

14 CC[C@H](O)c1ccccc1 (cannot buy) + c1ccccc1 ($1.0/g) → ?

15 CC[C@H](OS(=O)(=O)c1ccc(C)cc1)c1ccccc1 (cannot buy) + Oc1ccccc1 ($1.0/g) → ?

16 CC[C@H]([O-])c1ccccc1 (cannot buy) + Clc1ccccc1 ($1.0/g) → ?

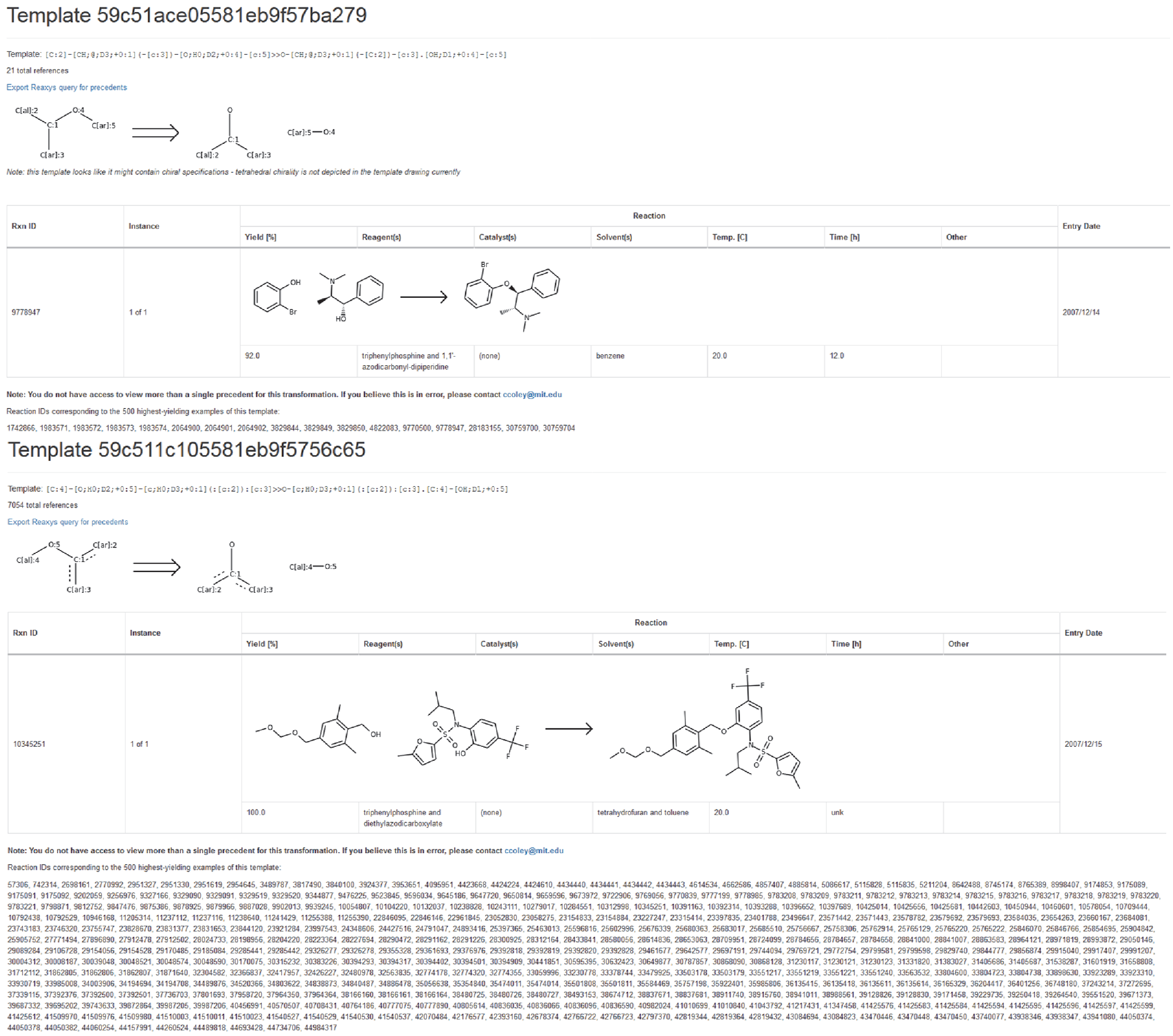
17 CC[C@H](OS(=O)(=O)c1ccc(C)cc1)c1ccccc1 (cannot buy) + [O-]c1ccccc1 ($1.0/g) → ?

18 CC[C@H](OC(=O)Oc1ccccc1)c1ccccc1 (cannot buy) → ?

19 CC[C@H](OS(=O)(=O)c1ccccc1)c1ccccc1 (cannot buy) + Oc1ccccc1 ($1.0/g) → ?

20 CC[C@H](OP(c1ccccc1)c1ccccc1)c1ccccc1 (cannot buy) + Oc1ccccc1 ($1.0/g) → ?

Figure S10. Retrosynthetic planning of a chiral aryl ether in MIT's ASKCOS system. Several suggestions relying on S_N2 displacements (#1, #12, #13, #15, #17, #19 and #20) use substrates corresponding to chemically incorrect stereoretentive process. Additionally, the oxidative alkoxylation proposed as #14 is feasible only when appropriate metal-coordinating group is present in the substrate to facilitate C-H activation. The reaction template for this transformation (see **Figure S12**) does not take into account this requirement.



Template 59c51ace05581eb9f57ba279

Template: `[C:2]-[CH;@;D3;+0:1](-[c:3])-[O;H0;D2;+0:4]-[c:5]>>O-[CH;@;D3;+0:1](-[C:2])-[c:3].[OH;D1;+0:4]-[c:5]`

21 total references

Export Reaxys query for precedents

Note: this template looks like it might contain chiral specifications - tetrahedral chirality is not depicted in the template drawing currently

Rxn ID	Instance	Reaction							Entry Date
		Yield [%]	Reagent(s)	Catalyst(s)	Solvent(s)	Temp. [C]	Time [h]	Other	
9778947	1 of 1								2007/12/14
		92.0	triphenylphosphine and 1,1'-azodicarbonyl-dipiperidine	(none)	benzene	20.0	12.0		

Note: You do not have access to view more than a single precedent for this transformation. If you believe this is in error, please contact ccoley@mit.edu

Reaction IDs corresponding to the 500 highest-yielding examples of this template:

1742866, 1983571, 1983572, 1983573, 1983574, 2064900, 2064901, 2064902, 3829844, 3829849, 3829850, 4822083, 9770500, 9778947, 28183155, 30759700, 30759704

Template 59c511c105581eb9f5756c65

Template: `[C:4]-[O;H0;D2;+0:5]-[c;H0;D3;+0:1](:[c:2]):[c:3]>>O-[c;H0;D3;+0:1](:[c:2]):[c:3].[C:4]-[OH;D1;+0:5]`

7054 total references

Export Reaxys query for precedents

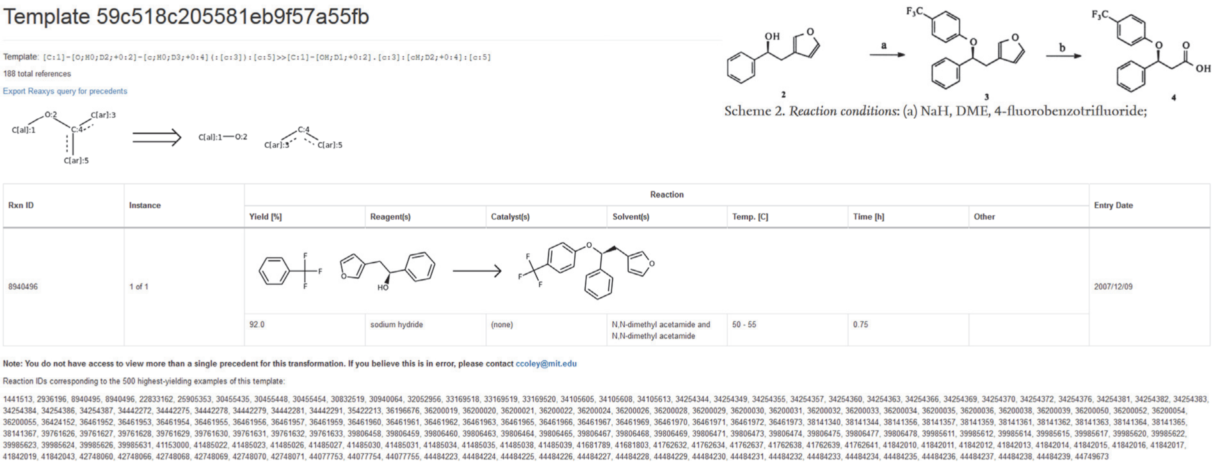
Rxn ID	Instance	Reaction							Entry Date
		Yield [%]	Reagent(s)	Catalyst(s)	Solvent(s)	Temp. [C]	Time [h]	Other	
10345251	1 of 1								2007/12/15
		100.0	triphenylphosphine and diethylazodicarboxylate	(none)	tetrahydrofuran and toluene	20.0	unk		

Note: You do not have access to view more than a single precedent for this transformation. If you believe this is in error, please contact ccoley@mit.edu

Reaction IDs corresponding to the 500 highest-yielding examples of this template:

57306, 742314, 2698161, 2770992, 2951327, 2951330, 2951619, 2954645, 3489787, 3817490, 3840100, 3924377, 3953651, 4095951, 4423668, 4424224, 4424610, 4434440, 4434441, 4434442, 4434443, 4614534, 4662586, 4857407, 4885814, 5086617, 5115828, 5115835, 5211204, 8642488, 8745174, 8765389, 8998407, 9174853, 9175089, 9175091, 9175092, 9202059, 9256976, 9327166, 9329090, 9329091, 9329519, 9329520, 9344877, 9476225, 9523845, 9596034, 9645186, 9647720, 9650814, 9659596, 9673972, 9722906, 9769056, 9770839, 9777199, 9778985, 9783208, 9783209, 9783211, 9783212, 9783213, 9783214, 9783215, 9783216, 9783217, 9783218, 9783219, 9783220, 9783221, 9798871, 9812752, 9847476, 9875386, 9878925, 9879966, 9887028, 9902013, 9939245, 10054807, 10104220, 10132037, 10238828, 10243111, 10279017, 10284551, 10312998, 10345251, 10391163, 10392314, 10393288, 10396652, 10397689, 10425014, 10425656, 10425681, 10442603, 10450944, 10460601, 10578054, 10709444, 10792438, 10792529, 10946168, 11205314, 11237112, 11237116, 11238640, 11241429, 11255388, 11255390, 22846095, 22846146, 22961845, 23052830, 23058275, 23154833, 23154884, 23227247, 23315414, 23397835, 23401788, 23496647, 23571442, 23571443, 23578782, 23579692, 23579693, 23584035, 23654263, 23660167, 23684081, 23743183, 23746320, 23755747, 23828670, 23831377, 23831653, 23844120, 23921284, 23997543, 24348606, 24427516, 24791047, 24893416, 25397365, 25463013, 25596816, 25602996, 25676339, 25680363, 25683017, 25685510, 25756667, 25758306, 25762914, 25765129, 25765220, 25765222, 25846070, 25846766, 25854695, 25904842, 25905752, 27771494, 27896890, 27912478, 27912502, 28024733, 28198956, 28204220, 28223364, 28227694, 28290472, 28291162, 28291226, 28300925, 28312164, 28433841, 28580056, 28614836, 28653063, 28709951, 28724099, 28784656, 28784657, 28784658, 28841000, 28841007, 28863583, 28964121, 28971819, 28993872, 29050146, 29089284, 29106728, 29154056, 29154528, 29170485, 29185084, 29285441, 29285442, 29326277, 29326278, 29355328, 29361693, 29376976, 29392818, 29392819, 29392820, 29392828, 29461677, 29642577, 29697191, 29744094, 29769721, 29772754, 29799581, 29799598, 29829740, 29844777, 29856874, 29915040, 29917407, 29991207, 30004312, 30008187, 30039048, 30048521, 30048574, 30048590, 30170075, 30315232, 30383226, 30394293, 30394317, 30394402, 30394501, 30394909, 30441851, 30595395, 30632423, 30649877, 30787857, 30868090, 30868128, 31230117, 31230121, 31230123, 31331820, 31383027, 31405686, 31405687, 31538287, 31601919, 31658808, 31712112, 31862805, 31862806, 31862807, 31871640, 32304582, 32366837, 32417957, 32426227, 32480978, 32563835, 32774178, 32774320, 32774355, 33059996, 33230778, 33378744, 33479925, 33503178, 33503179, 33551217, 33551219, 33551221, 33551240, 33563532, 33804600, 33804723, 33804738, 33898630, 33923289, 33923310, 33930719, 33985008, 34003906, 34194694, 34194708, 34489876, 34520366, 34803622, 34838873, 34840487, 34886478, 35056638, 35354840, 35474011, 35474014, 35501808, 35501811, 35584469, 35757198, 35922401, 35985806, 36135415, 36135418, 36135611, 36135614, 36165329, 36204417, 36401256, 36748180, 37243214, 37272695, 37339115, 37392376, 37392500, 37392501, 37736703, 37801693, 37958720, 37964350, 37964364, 38166160, 38166161, 38166164, 38480725, 38480726, 38480727, 38493153, 38674712, 38837671, 38837681, 38911740, 38915760, 38941011, 38988561, 39128826, 39128830, 39171458, 39229735, 39250418, 39264540, 39551520, 39671373, 39687332, 39695202, 39743633, 39872864, 39987205, 39987206, 40456991, 40570507, 40708431, 40764186, 40777075, 40777890, 40805614, 40836035, 40836066, 40836096, 40836590, 40982024, 41010699, 41010840, 41043792, 41217431, 41347458, 41425576, 41425583, 41425584, 41425594, 41425595, 41425596, 41425597, 41425599, 41425612, 41509970, 41509976, 41509980, 41510003, 41510011, 41510023, 41540527, 41540529, 41540530, 41540537, 42070484, 42176577, 42393160, 42678374, 42766722, 42766723, 42797370, 42819344, 42819364, 42819432, 43084694, 43084823, 43470446, 43470448, 43470450, 43740077, 43938346, 43938347, 43941080, 44050374, 44050378, 44050382, 44060254, 44157991, 44260524, 44489818, 44693428, 44734706, 44984317

Figure S11. Automatically extracted templates for Mitsunobu displacement with a phenol nucleophile in the ASKCOS software. Top: This reaction occurs with inversion of configuration. Stereoretentive process is feasible only when anchimeric assistance (here, from a tertiary amine present in the specific literature precedent but missing in the extracted reaction transform) is possible. Bottom: The reaction template extracted from a large number of examples (>7000) also does not account for inversion of configuration for secondary alcohols.



Scheme 2. *Reaction conditions*: (a) NaH, DME, 4-fluorobenzotrifluoride;

Template 59c518c205581eb9f57a55fb

Template: `[C:1]-[O;H0;D2;+0:2]-[c;H0;D3;+0:4](:[c:3]):[c:5]>>[C:1]-[OH;D1;+0:2].[c:3]:[cH;D2;+0:4]:[c:5]`

188 total references

Export Reaxys query for precedents

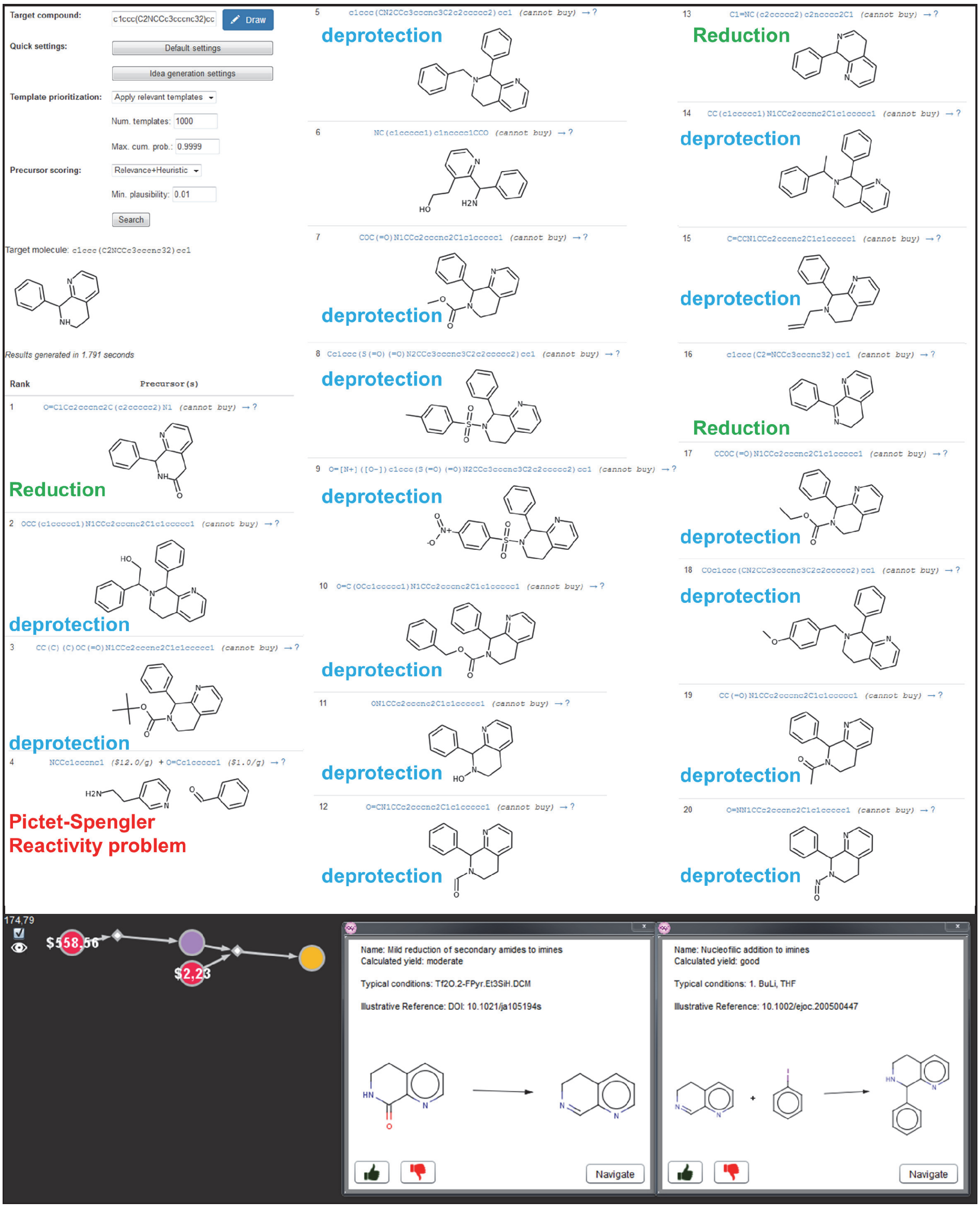
Rxn ID	Instance	Reaction							Entry Date
		Yield [%]	Reagent(s)	Catalyst(s)	Solvent(s)	Temp. [C]	Time [h]	Other	
8940496	1 of 1								2007/12/09
		92.0	sodium hydride	(none)	N,N-dimethyl acetamide and N,N-dimethyl acetamide	50 - 55	0.75		

Note: You do not have access to view more than a single precedent for this transformation. If you believe this is in error, please contact ccoley@mit.edu

Reaction IDs corresponding to the 500 highest-yielding examples of this template:

1441513, 2936196, 8940495, 8940496, 22833162, 25905353, 30455435, 30455448, 30455454, 30832519, 30940064, 32052956, 33169518, 33169519, 33169520, 34105605, 34105608, 34105613, 34254344, 34254349, 34254355, 34254357, 34254360, 34254363, 34254366, 34254369, 34254370, 34254372, 34254376, 34254381, 34254382, 34254383, 34254384, 34254386, 34254387, 34442272, 34442275, 34442278, 34442279, 34442281, 34442291, 35422213, 36196676, 36200019, 36200020, 36200021, 36200022, 36200024, 36200026, 36200028, 36200029, 36200030, 36200031, 36200032, 36200033, 36200034, 36200035, 36200036, 36200038, 36200039, 36200050, 36200052, 36200054, 36200055, 36424152, 36461952, 36461953, 36461954, 36461955, 36461956, 36461957, 36461959, 36461960, 36461961, 36461962, 36461963, 36461965, 36461966, 36461967, 36461969, 36461970, 36461971, 36461972, 36461973, 38141340, 38141344, 38141356, 38141357, 38141359, 38141361, 38141362, 38141363, 38141364, 38141365, 38141367, 39761626, 39761627, 39761628, 39761629, 39761630, 39761631, 39761632, 39761633, 39806458, 39806459, 39806460, 39806463, 39806464, 39806465, 39806467, 39806468, 39806469, 39806471, 39806473, 39806474, 39806475, 39806477, 39806478, 39985611, 39985612, 39985614, 39985615, 39985617, 39985620, 39985622, 39985623, 39985624, 39985626, 39985631, 41153000, 41485022, 41485023, 41485026, 41485027, 41485030, 41485031, 41485034, 41485035, 41485038, 41485039, 41681789, 41681803, 41762632, 41762634, 41762637, 41762638, 41762639, 41762641, 41842010, 41842011, 41842012, 41842013, 41842014, 41842015, 41842016, 41842017, 41842019, 41842043, 42748060, 42748066, 42748068, 42748069, 42748070, 42748071, 44077753, 44077754, 44077755, 44484223, 44484224, 44484225, 44484226, 44484227, 44484228, 44484229, 44484230, 44484231, 44484232, 44484233, 44484234, 44484235, 44484236, 44484237, 44484238, 44484239, 44749673

Figure S12. Automatically extracted core of oxidative alkoxylation in the ASKCOS software. The proposed process is feasible only if appropriate metal-coordinating group (usually pyridine, *N*-heterocycle, or amide) is present in the substrate. Additionally, the literature precedent used to support this reaction template (bottom) was erroneously deposited in the database and misses fluoride atom being substituted in S_NAr process in the original publication (inset in top-right part).



Target compound: c1ccc(C2NCCc3cccnc32)cc

Quick settings: Default settings | Idea generation settings

Template prioritization: Apply relevant templates

Num. templates: 1000

Max. cum. prob.: 0.9999

Precursor scoring: Relevance+Heuristic

Min. plausibility: 0.01

Target molecule: c1ccc(C2NCCc3cccnc32)cc1

Results generated in 1.791 seconds

Rank Precursor(s)

1 O=C1Cc2cccnc2C(c2ccccc2)N1 *(cannot buy)* → ?

2 OCC(c1ccccc1)N1CCc2cccnc2C1c1ccccc1 *(cannot buy)* → ?

3 CC(C)(C)OC(=O)N1CCc2cccnc2C1c1ccccc1 *(cannot buy)* → ?

4 NCCc1cccnc1 *($12.0/g)* + O=Cc1ccccc1 *($1.0/g)* → ?

5 c1ccc(CN2CCc3cccnc3C2c2ccccc2)cc1 *(cannot buy)* → ?

6 NC(c1ccccc1)c1ncccc1CCO *(cannot buy)* → ?

7 COC(=O)N1CCc2cccnc2C1c1ccccc1 *(cannot buy)* → ?

8 Cc1ccc(S(=O)(=O)N2CCc3cccnc3C2c2ccccc2)cc1 *(cannot buy)* → ?

9 O=[N+]([O-])c1ccc(S(=O)(=O)N2CCc3cccnc3C2c2ccccc2)cc1 *(cannot buy)* → ?

10 O=C(OCc1ccccc1)N1CCc2cccnc2C1c1ccccc1 *(cannot buy)* → ?

11 ON1CCc2cccnc2C1c1ccccc1 *(cannot buy)* → ?

12 O=CN1CCc2cccnc2C1c1ccccc1 *(cannot buy)* → ?

13 C1=NC(c2ccccc2)c2ncccc2C1 *(cannot buy)* → ?

14 CC(c1ccccc1)N1CCc2cccnc2C1c1ccccc1 *(cannot buy)* → ?

15 C=CCN1CCc2cccnc2C1c1ccccc1 *(cannot buy)* → ?

16 c1ccc(C2=NCCc3cccnc32)cc1 *(cannot buy)* → ?

17 CCOC(=O)N1CCc2cccnc2C1c1ccccc1 *(cannot buy)* → ?

18 COc1ccc(CN2CCc3cccnc3C2c2ccccc2)cc1 *(cannot buy)* → ?

19 CC(=O)N1CCc2cccnc2C1c1ccccc1 *(cannot buy)* → ?

20 O=NN1CCc2cccnc2C1c1ccccc1 *(cannot buy)* → ?

Name: Mild reduction of secondary amides to imines
Calculated yield: moderate

Typical conditions: Tf2O.2-FPyr.Et3SiH.DCM

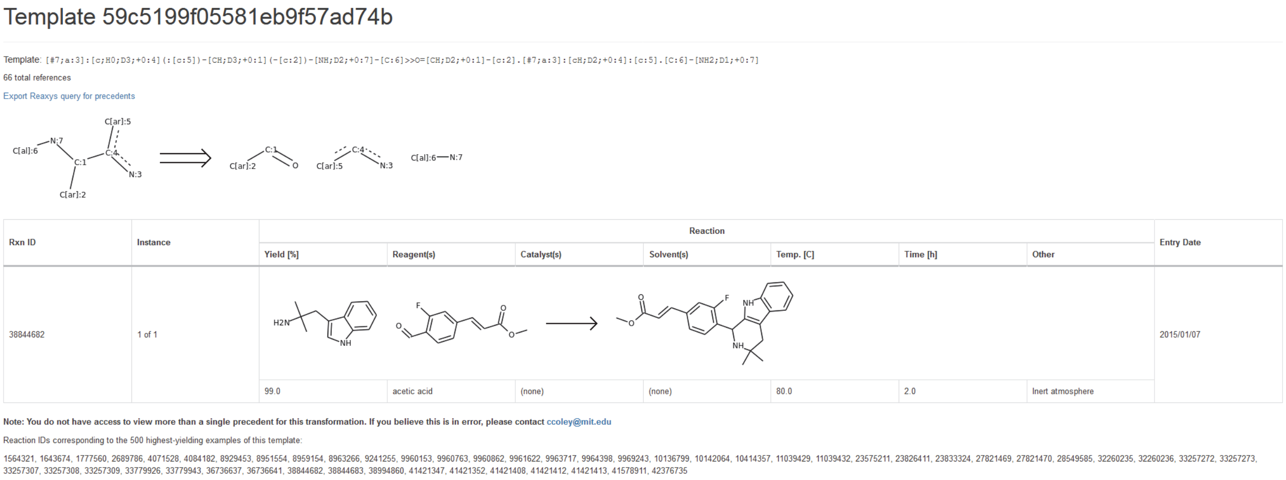
Illustrative Reference: DOI: 10.1021/ja105194s

Name: Nucleofilic addition to imines
Calculated yield: good

Typical conditions: 1. BuLi, THF

Illustrative Reference: 10.1002/ejoc.200500447

Figure S13. Retrosynthetic planning of tetrahydroisoquinoline in MIT's ASKCOS system. Several of the top-scoring solutions are limited to removals of different protecting groups or reductions of an amide (#1) or cyclic imines (#13,#16). The automatically extracted reaction template (see **Figure S14**) for Pictet-Spengler cyclisation (#4) is too general and lacks information regarding the type of the reacting aromatic system. This reaction is limited to electron-rich arenes and heteroarenes while ASKCOS allows for the annulation of electron-poor pyridine. Bottom: In contrast, Chematica's top-scoring solution commences with reduction of a commercially available amide to imine and subsequent addition of an organometallic reagent derived from iodobenzene.



Template 59c5199f05581eb9f57ad74b

Template: `[#7;a:3]:[c;H0;D3;+0:4](:[c:5])-[CH;D3;+0:1](-[c:2])-[NH;D2;+0:7]-[C:6]>>O=[CH;D2;+0:1]-[c:2].[#7;a:3]:[cH;D2;+0:4]:[c:5].[C:6]-[NH2;D1;+0:7]`

66 total references

Export Reaxys query for precedents

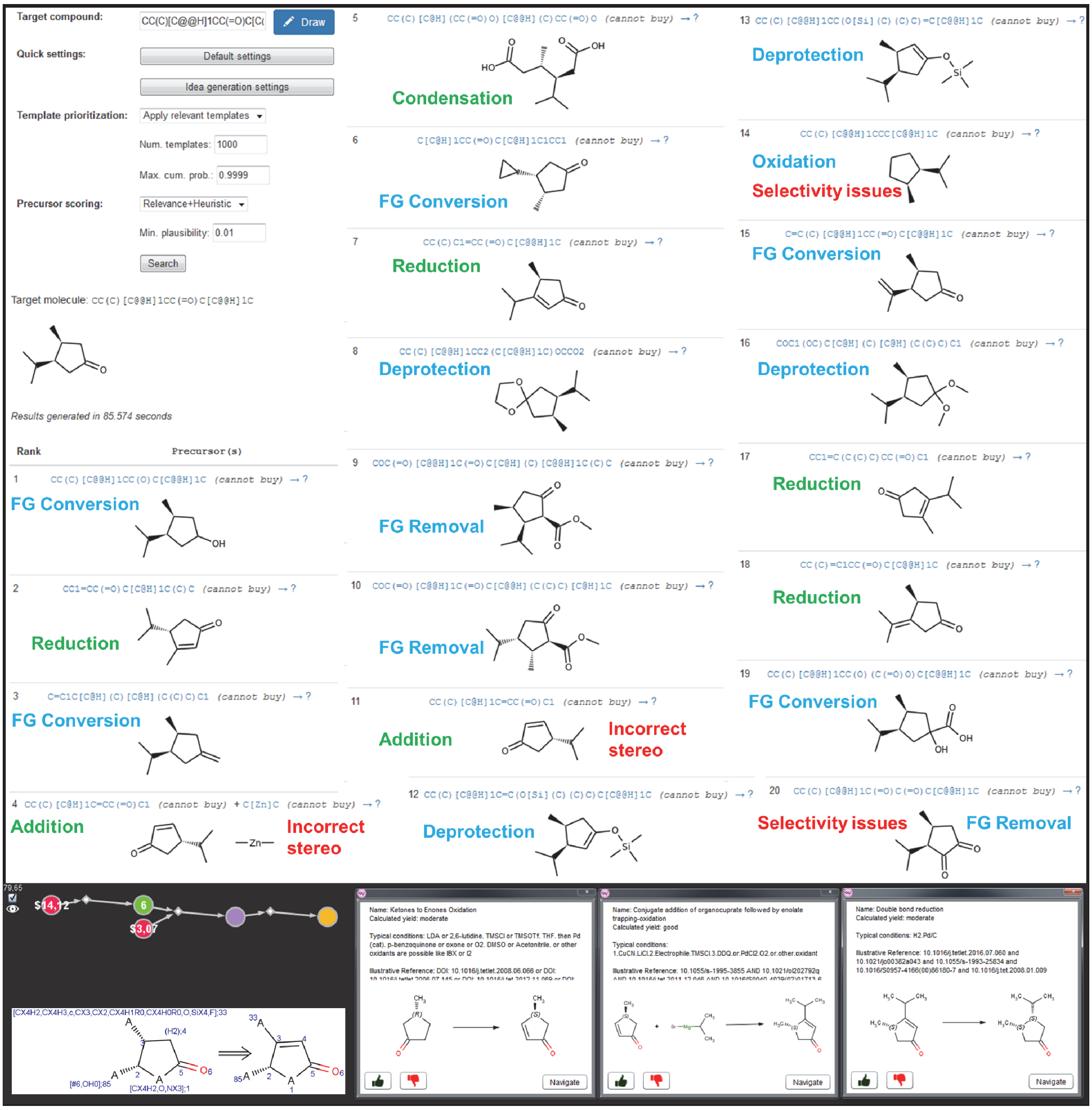
Rxn ID	Instance	Reaction							Entry Date
		Yield [%]	Reagent(s)	Catalyst(s)	Solvent(s)	Temp. [C]	Time [h]	Other	
38844682	1 of 1	99.0	acetic acid	(none)	(none)	80.0	2.0	Inert atmosphere	2015/01/07

Note: You do not have access to view more than a single precedent for this transformation. If you believe this is in error, please contact ccoley@mit.edu

Reaction IDs corresponding to the 500 highest-yielding examples of this template:

1564321, 1643674, 1777560, 2689786, 4071528, 4084182, 8929453, 8951554, 8959154, 8963266, 9241255, 9960153, 9960763, 9960862, 9961622, 9963717, 9964398, 9969243, 10136799, 10142064, 10414357, 11039429, 11039432, 23575211, 23826411, 23833324, 27821469, 27821470, 28549585, 32260235, 32260236, 33257272, 33257273, 33257307, 33257308, 33257309, 33779926, 33779943, 36736637, 36736641, 38844682, 38844683, 38994860, 41421347, 41421352, 41421408, 41421412, 41421413, 41578911, 42376735

Figure S14. Automatically extracted core of Pictet-Spengler cyclisation from the ASKCOS software incorrectly allowing for the annulation of electron poor heteroarenes (here, pyridine in example from **Figure S13**).



Target compound: CC(C)[C@@H]1CC(=O)C[C(

Quick settings: Default settings

Idea generation settings

Template prioritization: Apply relevant templates

Num. templates: 1000

Max. cum. prob.: 0.9999

Precursor scoring: Relevance+Heuristic

Min. plausibility: 0.01

Target molecule: CC(C)[C@@H]1CC(=O)C[C@@H]1C

Results generated in 85.574 seconds

Rank	Precursor(s)
1	CC(C)[C@@H]1CC(O)C[C@@H]1C *(cannot buy)* → ?
2	CC1=CC(=O)C[C@H]1C(C)C *(cannot buy)* → ?
3	C=C1C[C@H](C)[C@H](C(C)C)C1 *(cannot buy)* → ?
4	CC(C)[C@H]1C=CC(=O)C1 *(cannot buy)* + C[Zn]C *(cannot buy)* → ?
5	CC(C)[C@H](CC(=O)O)[C@@H](C)CC(=O)O *(cannot buy)* → ?
6	C[C@H]1CC(=O)C[C@H]1C1CC1 *(cannot buy)* → ?
7	CC(C)C1=CC(=O)C[C@@H]1C *(cannot buy)* → ?
8	CC(C)[C@@H]1CC2(C[C@@H]1C)OCCO2 *(cannot buy)* → ?
9	COC(=O)[C@@H]1C(=O)C[C@H](C)[C@@H]1C(C)C *(cannot buy)* → ?
10	COC(=O)[C@@H]1C(=O)C[C@@H](C(C)C)[C@H]1C *(cannot buy)* → ?
11	CC(C)[C@H]1C=CC(=O)C1 *(cannot buy)* → ?
12	CC(C)[C@@H]1C=C(O[Si](C)(C)C)C[C@@H]1C *(cannot buy)* → ?
13	CC(C)[C@@H]1CC(O[Si](C)(C)C)=C[C@@H]1C *(cannot buy)* → ?
14	CC(C)[C@@H]1CCC[C@@H]1C *(cannot buy)* → ?
15	C=C(C)[C@@H]1CC(=O)C[C@@H]1C *(cannot buy)* → ?
16	COC1(OC)C[C@H](C)[C@H](C(C)C)C1 *(cannot buy)* → ?
17	CC1=C(C(C)C)CC(=O)C1 *(cannot buy)* → ?
18	CC(C)=C1CC(=O)C[C@@H]1C *(cannot buy)* → ?
19	CC(C)[C@@H]1CC(O)(C(=O)O)C[C@@H]1C *(cannot buy)* → ?
20	CC(C)[C@@H]1C(=O)C(=O)C[C@@H]1C *(cannot buy)* → ?

Name: Ketones to Enones Oxidation
Calculated yield: moderate

Typical conditions: LDA or 2,6-lutidine. TMSCl or TMSOTf. THF. then Pd (cat). p-benzoquinone or oxone or O2. DMSO or Acetonitrile. or other oxidants are possible like IBX or I2

Illustrative Reference: DOI: 10.1016/j.tetlet.2008.06.066 or DOI:

Name: Conjugate addition of organocuprate followed by enolate trapping-oxidation
Calculated yield: good

Typical conditions:
1.CuCN.LiCl.2.Electrophile.TMSCl.3.DDQ.or.PdCl2.O2.or.other.oxidant

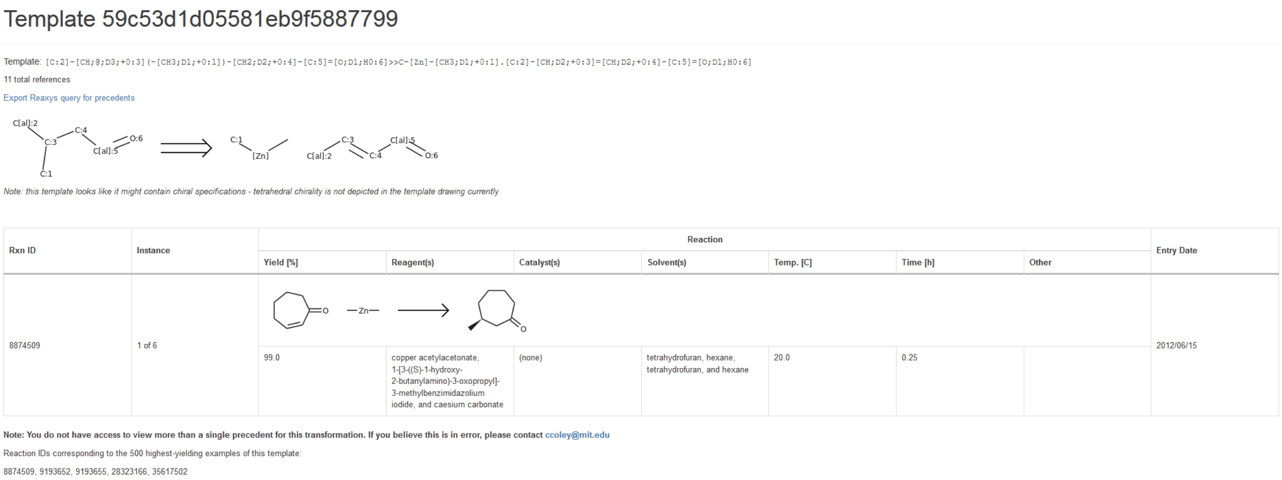
Illustrative Reference: 10.1055/s-1995-3855 AND 10.1021/ol202792q

Name: Double bond reduction
Calculated yield: moderate

Typical conditions: H2.Pd/C

Illustrative Reference: 10.1016/j.tetlet.2016.07.060 and 10.1021/jo00382a043 and 10.1055/s-1993-25834 and 10.1016/S0957-4166(00)86180-7 and 10.1016/j.tet.2008.01.009

Figure S15. Retrosynthetic planning of chiral *cis* cyclopentanone in MIT's ASKCOS system. The reaction template (see **Figure S16**) for chiral conjugated addition of an organometallic reagent to an enone (#4) does not account for the presence of mismatched substituents and allows for chemically incorrect *syn*-selective process. None of the 14 reaction templates (see **Figures S18-S22**) for substrate-controlled reductions of alkenes (#2, #7, #17, #18) accounts for the necessary structural features controlling the reaction's outcome. Bottom: In Chematica's solution, the desired 1,2-*cis* cyclopentanone is constructed via addition of an organometallic reagent followed by trapping and oxidation of an enolate and substrate-controlled reduction of an alkene. In sharp contrast to automatically extracted rules (cf. **Figures S18-S22**), the expert-coded template (shown in the inset in the bottom-left part of the Figure) accounts for the presence of substituents dictating the stereoselective reaction's outcome.



Template 59c53d1d05581eb9f5887799

Template: `[C:2]-[CH;@;D3;+0:3](-[CH3;D1;+0:1])-[CH2;D2;+0:4]-[C:5]=[O;D1;H0:6]>>C-[Zn]-[CH3;D1;+0:1].[C:2]-[CH;D2;+0:3]=[CH;D2;+0:4]-[C:5]=[O;D1;H0:6]`

11 total references

Export Reaxys query for precedents

Note: this template looks like it might contain chiral specifications - tetrahedral chirality is not depicted in the template drawing currently

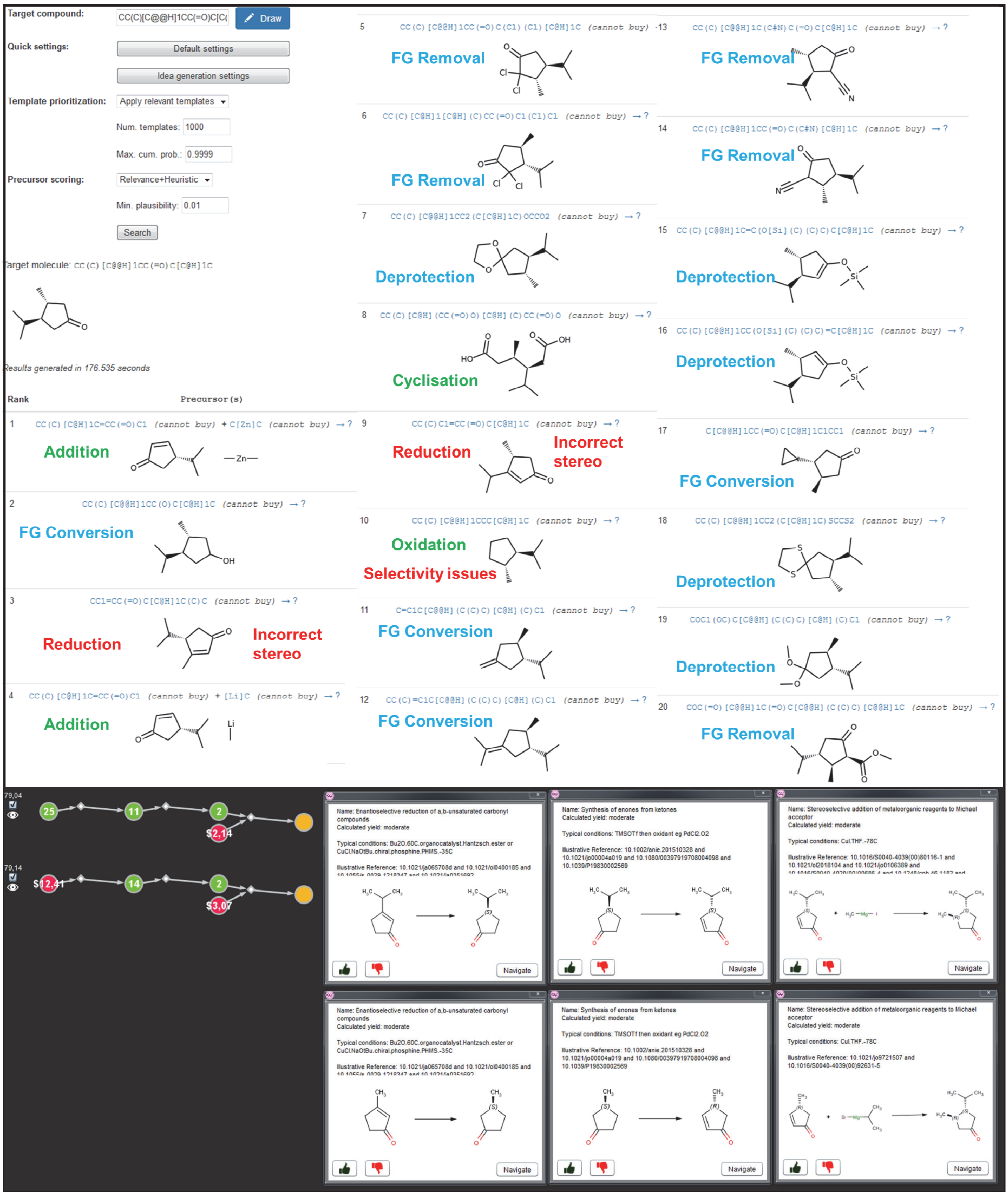
Rxn ID	Instance	Reaction							Entry Date
		Yield [%]	Reagent(s)	Catalyst(s)	Solvent(s)	Temp. [C]	Time [h]	Other	
8874509	1 of 6	99.0	copper acetylacetonate, 1-[3-((S)-1-hydroxy-2-butanylamino)-3-oxopropyl]-3-methylbenzimidazolium iodide, and caesium carbonate	(none)	tetrahydrofuran, hexane, tetrahydrofuran, and hexane	20.0	0.25		2012/06/15

Note: You do not have access to view more than a single precedent for this transformation. If you believe this is in error, please contact ccoley@mit.edu

Reaction IDs corresponding to the 500 highest-yielding examples of this template:

8874509, 9193652, 9193655, 28323166, 35617502

Figure S16. ASKCOS' automatically extracted core of a chiral-catalyst-controlled conjugated addition allows for mismatched substrates.



Target compound: CC(C)[C@@H]1CC(=O)C[C(

Quick settings:

Template prioritization: Apply relevant templates

Num. templates: 1000

Max. cum. prob.: 0.9999

Precursor scoring: Relevance+Heuristic

Min. plausibility: 0.01

Target molecule: CC(C)[C@@H]1CC(=O)C[C@H]1C

Results generated in 176.535 seconds

Rank Precursor(s)

1 CC(C)[C@H]1C=CC(=O)C1 (cannot buy) + C[Zn]C (cannot buy) → ? Addition

2 CC(C)[C@@H]1CC(O)C[C@H]1C (cannot buy) → ? FG Conversion

3 CC1=CC(=O)C[C@H]1C(C)C (cannot buy) → ? Reduction Incorrect stereo

4 CC(C)[C@H]1C=CC(=O)C1 (cannot buy) + [Li]C (cannot buy) → ? Addition

5 CC(C)[C@@H]1CC(=O)C(Cl)(Cl)[C@H]1C (cannot buy) FG Removal

6 CC(C)[C@H]1[C@H](C)CC(=O)C1(Cl)Cl (cannot buy) → ? FG Removal

7 CC(C)[C@@H]1CC2(C[C@H]1C)OCCO2 (cannot buy) → ? Deprotection

8 CC(C)[C@H](CC(=O)O)[C@H](C)CC(=O)O (cannot buy) → ? Cyclisation

9 CC(C)C1=CC(=O)C[C@H]1C (cannot buy) → ? Reduction Incorrect stereo

10 CC(C)[C@@H]1CCC[C@H]1C (cannot buy) → ? Oxidation Selectivity issues

11 C=C1C[C@@H](C(C)C)[C@H](C)C1 (cannot buy) → ? FG Conversion

12 CC(C)=C1C[C@@H](C(C)C)[C@H](C)C1 (cannot buy) → ? FG Conversion

13 CC(C)[C@@H]1C(C#N)C(=O)C[C@H]1C (cannot buy) → ? FG Removal

14 CC(C)[C@@H]1CC(=O)C(C#N)[C@H]1C (cannot buy) → ? FG Removal

15 CC(C)[C@@H]1C=C(O[Si](C)(C)C)C[C@H]1C (cannot buy) → ? Deprotection

16 CC(C)[C@@H]1CC(O[Si](C)(C)C)=C[C@H]1C (cannot buy) → ? Deprotection

17 C[C@@H]1CC(=O)C[C@H]1C1CC1 (cannot buy) → ? FG Conversion

18 CC(C)[C@@H]1CC2(C[C@H]1C)SCCS2 (cannot buy) → ? Deprotection

19 COC1(OC)C[C@@H](C(C)C)[C@H](C)C1 (cannot buy) → ? Deprotection

20 COC(=O)[C@@H]1C(=O)C[C@@H](C(C)C)[C@@H]1C (cannot buy) → ? FG Removal

Name: Enantioselective reduction of a,b-unsaturated carbonyl compounds
Calculated yield: moderate

Typical conditions: Bu2O.60C.organocatalyst.Hantzsch.ester or CuCl.NaOtBu.chiral.phosphine.PHMS.-35C

Illustrative Reference: 10.1021/ja065708d and 10.1021/ol0400185 and

Name: Synthesis of enones from ketones
Calculated yield: moderate

Typical conditions: TMSOTf then oxidant eg PdCl2.O2

Illustrative Reference: 10.1002/anie.201510328 and 10.1021/jo00004a019 and 10.1080/00397919708004098 and 10.1039/P19830002569

Name: Stereoselective addition of metaloorganic reagents to Michael acceptor
Calculated yield: moderate

Typical conditions: CuI.THF.-78C

Illustrative Reference: 10.1016/S0040-4039(00)80116-1 and 10.1021/ol2018104 and 10.1021/jo0106389 and

Name: Enantioselective reduction of a,b-unsaturated carbonyl compounds
Calculated yield: moderate

Typical conditions: Bu2O.60C.organocatalyst.Hantzsch.ester or CuCl.NaOtBu.chiral.phosphine.PHMS.-35C

Illustrative Reference: 10.1021/ja065708d and 10.1021/ol0400185 and

Name: Synthesis of enones from ketones
Calculated yield: moderate

Typical conditions: TMSOTf then oxidant eg PdCl2.O2

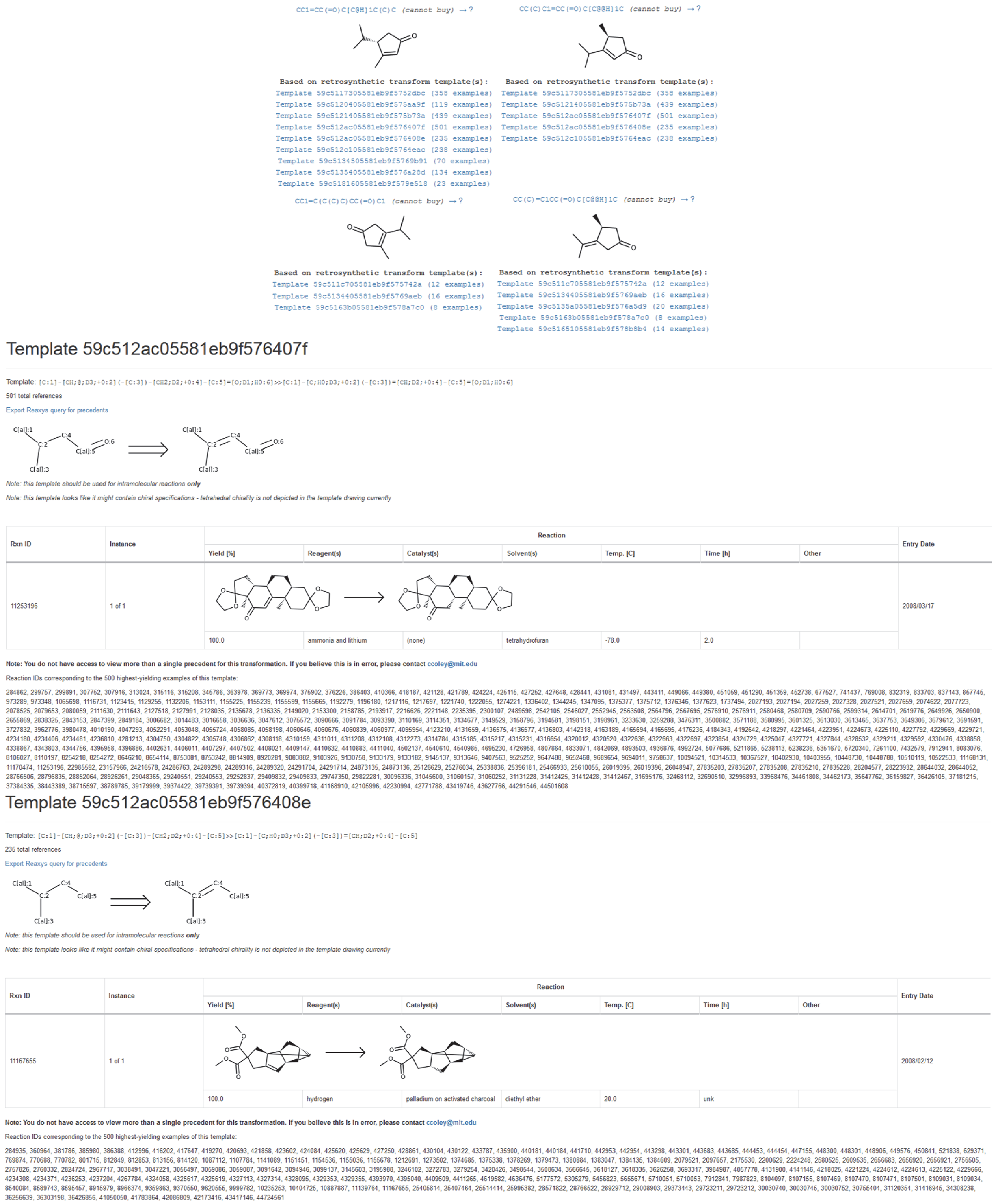
Illustrative Reference: 10.1002/anie.201510328 and 10.1021/jo00004a019 and 10.1080/00397919708004098 and 10.1039/P19830002569

Name: Stereoselective addition of metaloorganic reagents to Michael acceptor
Calculated yield: moderate

Typical conditions: CuI.THF.-78C

Illustrative Reference: 10.1021/jo9721507 and 10.1016/S0040-4039(00)92631-5

Figure S17. Retrosynthetic planning of chiral *trans*-cyclopentanone in MIT's ASKCOS system. None of the 14 reaction templates (see **Figures S18-S22**) for substrate-controlled reductions of alkenes (#2, #7, #17, #18) accounts for the necessary structural features controlling the reaction's outcome and allows for chemically incorrect process leading to the *trans* product. Bottom: In Chematica's top-scoring suggestions, the desired 1,2-*trans* configuration is achieved enantioselectively via reduction of an enone, subsequent Saegusa type reoxidation, and substrate-controlled addition of an organometallic reagent.



CC1=CC(=O)C[C@H]1C(C)C *(cannot buy)* → ?

Based on retrosynthetic transform template(s):
Template 59c5117305581eb9f5752dbc (358 examples)
Template 59c5120405581eb9f575aa9f (119 examples)
Template 59c5121405581eb9f575b73a (439 examples)
Template 59c512ac05581eb9f576407f (501 examples)
Template 59c512ac05581eb9f576408e (235 examples)
Template 59c512c105581eb9f5764eac (238 examples)
Template 59c5134505581eb9f5769b91 (70 examples)
Template 59c5135405581eb9f576a28d (134 examples)
Template 59c5181605581eb9f579e518 (23 examples)

CC(C)C1=CC(=O)C[C@@H]1C *(cannot buy)* → ?

Based on retrosynthetic transform template(s):
Template 59c5117305581eb9f5752dbc (358 examples)
Template 59c5121405581eb9f575b73a (439 examples)
Template 59c512ac05581eb9f576407f (501 examples)
Template 59c512ac05581eb9f576408e (235 examples)
Template 59c512c105581eb9f5764eac (238 examples)

CC1=C(C(C)C)CC(=O)C1 *(cannot buy)* → ?

Based on retrosynthetic transform template(s):
Template 59c511c705581eb9f575742a (12 examples)
Template 59c5134405581eb9f5769aeb (16 examples)
Template 59c5163b05581eb9f578a7c0 (8 examples)

CC(C)=C1CC(=O)C[C@@H]1C *(cannot buy)* → ?

Based on retrosynthetic transform template(s):
Template 59c511c705581eb9f575742a (12 examples)
Template 59c5134405581eb9f5769aeb (16 examples)
Template 59c5135a05581eb9f576a5d9 (20 examples)
Template 59c5163b05581eb9f578a7c0 (8 examples)
Template 59c5165105581eb9f578b8b4 (14 examples)

Template 59c512ac05581eb9f576407f

Template: `[C:1]-[CH;@;D3;+0:2](-[C:3])-[CH2;D2;+0:4]-[C:5]=[O;D1;H0:6]>>[C:1]-[C;H0;D3;+0:2](-[C:3])=[CH;D2;+0:4]-[C:5]=[O;D1;H0:6]`

501 total references

Export Reaxys query for precedents

Note: this template should be used for intramolecular reactions ***only***

Note: this template looks like it might contain chiral specifications - tetrahedral chirality is not depicted in the template drawing currently

Rxn ID	Instance	Reaction							Entry Date
		Yield [%]	Reagent(s)	Catalyst(s)	Solvent(s)	Temp. [C]	Time [h]	Other	
11253196	1 of 1								2008/03/17
		100.0	ammonia and lithium	(none)	tetrahydrofuran	-78.0	2.0		

Note: You do not have access to view more than a single precedent for this transformation. If you believe this is in error, please contact ccoley@mit.edu

Reaction IDs corresponding to the 500 highest-yielding examples of this template:

284862, 299757, 299891, 307752, 307916, 313024, 315116, 315208, 345786, 363978, 369773, 369974, 375902, 376226, 386403, 410366, 418187, 421128, 421789, 424224, 425115, 427252, 427648, 428441, 431081, 431497, 443411, 449066, 449380, 451059, 451290, 451359, 452738, 677527, 741437, 769008, 832319, 833703, 837143, 857745, 973289, 973348, 1065698, 1116731, 1123415, 1129255, 1132206, 1153111, 1155225, 1155239, 1155599, 1155665, 1192279, 1196180, 1217116, 1217697, 1221740, 1222055, 1274221, 1336402, 1344245, 1347095, 1375377, 1375712, 1376346, 1377623, 1737494, 2027193, 2027194, 2027259, 2027328, 2027521, 2027659, 2074622, 2077723, 2078525, 2079653, 2080059, 2111630, 2111643, 2127518, 2127991, 2128035, 2135678, 2136335, 2149020, 2153300, 2158785, 2193917, 2216626, 2221148, 2235395, 2300107, 2489598, 2542105, 2546027, 2552945, 2563508, 2564796, 2567695, 2576910, 2576911, 2580468, 2580709, 2590766, 2599314, 2614701, 2619776, 2649926, 2650900, 2655869, 2838325, 2843153, 2847399, 2849184, 3006682, 3014483, 3016658, 3036636, 3047612, 3075572, 3090666, 3091784, 3093390, 3110169, 3114351, 3134677, 3149529, 3158796, 3194581, 3198151, 3198961, 3233630, 3259288, 3476311, 3500882, 3571188, 3580995, 3601325, 3613030, 3613465, 3637753, 3649306, 3679612, 3691591, 3727832, 3962776, 3980478, 4010190, 4047293, 4052291, 4053048, 4055724, 4058085, 4058198, 4060646, 4060676, 4060839, 4060977, 4095954, 4123210, 4131659, 4136575, 4136577, 4136803, 4142318, 4163189, 4165694, 4165695, 4176236, 4184343, 4192642, 4218297, 4221464, 4223951, 4224673, 4225110, 4227792, 4229669, 4229721, 4234180, 4234406, 4234481, 4236810, 4281213, 4304750, 4304822, 4305748, 4306862, 4308118, 4310159, 4311011, 4311208, 4312108, 4312273, 4314784, 4315185, 4315217, 4315231, 4316654, 4320012, 4320520, 4322636, 4322663, 4322697, 4323854, 4324729, 4325047, 4327721, 4327844, 4328532, 4329211, 4329592, 4330476, 4338858, 4338867, 4343803, 4344756, 4395958, 4396886, 4402631, 4406011, 4407297, 4407502, 4408021, 4409147, 4410632, 4410883, 4411040, 4502137, 4540610, 4540985, 4695230, 4726958, 4807864, 4833071, 4842069, 4893503, 4936876, 4992724, 5077686, 5211865, 5238113, 5238236, 5351670, 5720340, 7261100, 7432579, 7912941, 8083076, 8106027, 8110197, 8254218, 8254272, 8646210, 8654114, 8753081, 8753242, 8814909, 8920281, 9083882, 9103926, 9130758, 9133179, 9133182, 9145137, 9313646, 9407563, 9525252, 9647488, 9652468, 9689654, 9694011, 9758637, 10094521, 10314533, 10367527, 10402930, 10403955, 10448730, 10448788, 10510119, 10522533, 11168131, 11170474, 11253196, 22985592, 23157966, 24216578, 24286763, 24289298, 24289316, 24289320, 24291704, 24291714, 24873135, 24873136, 25126629, 25276034, 25338836, 25396181, 25466933, 25610055, 26019395, 26019396, 26048947, 27835203, 27835207, 27835208, 27835210, 27835228, 28204577, 28223932, 28644032, 28644052, 28766506, 28796835, 28852064, 28926261, 29048365, 29240551, 29240553, 29252837, 29409832, 29409833, 29747350, 29822281, 30096336, 31045600, 31060157, 31060252, 31131228, 31412425, 31412428, 31412467, 31695176, 32468112, 32690510, 32996893, 33968476, 34461808, 34462173, 35647762, 36159827, 36426105, 37181215, 37384335, 38443389, 38715597, 38789785, 39179999, 39374422, 39739391, 39739394, 40372819, 40399718, 41168910, 42105996, 42230994, 42771788, 43419746, 43627766, 44291546, 44501608

Template 59c512ac05581eb9f576408e

Template: `[C:1]-[CH;@;D3;+0:2](-[C:3])-[CH2;D2;+0:4]-[C:5]>>[C:1]-[C;H0;D3;+0:2](-[C:3])=[CH;D2;+0:4]-[C:5]`

235 total references

Export Reaxys query for precedents

Note: this template should be used for intramolecular reactions ***only***

Note: this template looks like it might contain chiral specifications - tetrahedral chirality is not depicted in the template drawing currently

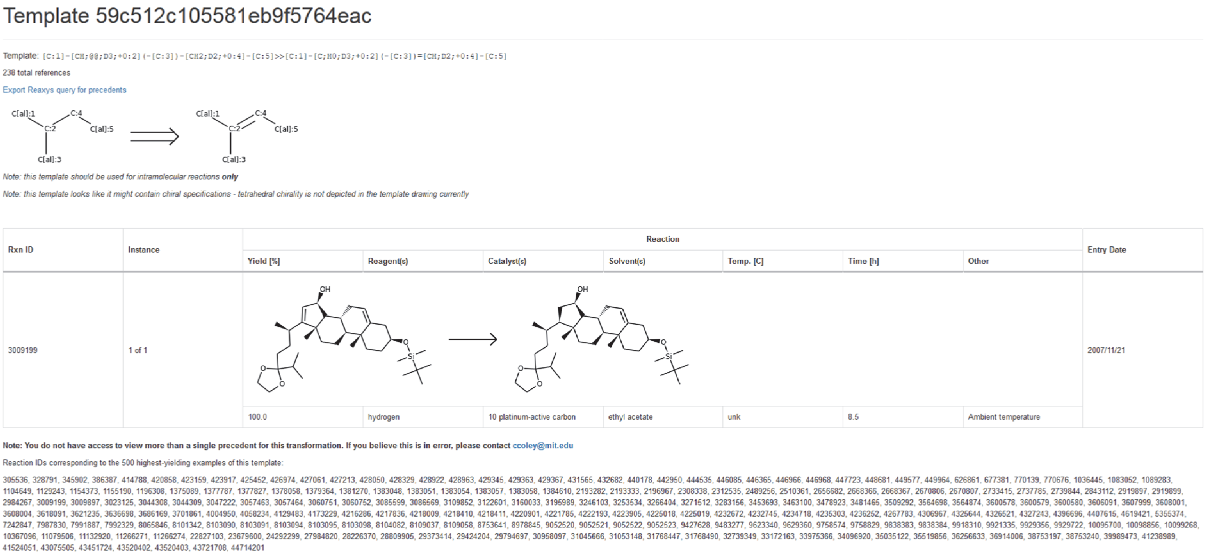
Rxn ID	Instance	Reaction							Entry Date
		Yield [%]	Reagent(s)	Catalyst(s)	Solvent(s)	Temp. [C]	Time [h]	Other	
11167655	1 of 1								2008/02/12
		100.0	hydrogen	palladium on activated charcoal	diethyl ether	20.0	unk		

Note: You do not have access to view more than a single precedent for this transformation. If you believe this is in error, please contact ccoley@mit.edu

Reaction IDs corresponding to the 500 highest-yielding examples of this template:

284935, 360964, 381786, 385980, 386388, 412996, 416202, 417647, 419270, 420693, 421858, 423602, 424084, 425620, 425629, 427250, 428861, 430104, 430122, 433787, 435900, 440181, 440184, 441710, 442953, 442954, 443298, 443301, 443683, 443685, 444453, 444454, 447155, 448300, 448301, 448906, 449576, 450841, 521838, 629371, 769874, 770688, 770782, 801715, 812849, 812853, 813156, 814120, 1087112, 1107784, 1141089, 1151451, 1154536, 1155036, 1155678, 1212691, 1273502, 1374685, 1375338, 1378269, 1379473, 1380884, 1383047, 1384135, 1384609, 2079521, 2097657, 2175530, 2200629, 2224248, 2580525, 2609535, 2656683, 2656920, 2656921, 2756505, 2757826, 2760332, 2824724, 2967717, 3038491, 3047221, 3056497, 3059086, 3059087, 3091642, 3094946, 3099137, 3145603, 3195988, 3246102, 3272783, 3279254, 3420426, 3498544, 3508634, 3566645, 3618127, 3618335, 3626258, 3693317, 3984987, 4057778, 4131900, 4141146, 4218025, 4221224, 4224612, 4224613, 4225122, 4229666, 4234308, 4234371, 4236253, 4237204, 4267784, 4324058, 4325617, 4325619, 4327113, 4327314, 4328095, 4329353, 4329355, 4393970, 4395040, 4409509, 4411265, 4619582, 4636476, 5177572, 5305279, 5456823, 5655671, 5710051, 5710053, 7912841, 7987823, 8104097, 8107155, 8107469, 8107470, 8107471, 8107501, 8109031, 8109034, 8540084, 8589743, 8595457, 8915979, 8966374, 9359863, 9370550, 9620555, 9999782, 10235253, 10404725, 10887887, 11139764, 11167655, 25405814, 25407464, 25514414, 25995382, 28571822, 28766522, 28929712, 29008903, 29373443, 29723211, 29723212, 30030740, 30030745, 30030752, 30755404, 31120354, 31416945, 34308238, 36256639, 36303198, 36426856, 41050050, 41783864, 42086809, 42173416, 43417146, 44724561

Figure S18. Reaction templates extracted from substrate-controlled reductions of alkenes. None of the 14 templates (with the remaining ones shown in **Figures S19-S22**) used to generate precursors for the chiral cyclopentanone from **Figure S15** accounts for necessary substituents dictating the reaction's stereoselective outcome.



Template 59c512c105581eb9f5764eac

Template: `[C:1]-[CH;@@;D3;+0:2](-[C:3])-[CH2;D2;+0:4]-[C:5]>>[C:1]-[C;H0;D3;+0:2](-[C:3])=[CH;D2;+0:4]-[C:5]`

238 total references

Export Reaxys query for precedents

Note: this template should be used for intramolecular reactions ***only***

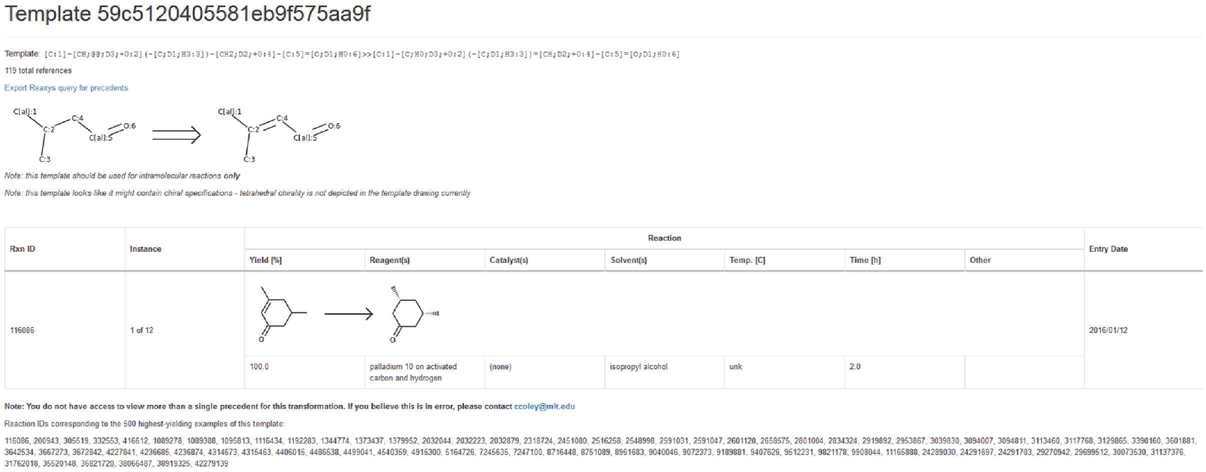
Note: this template looks like it might contain chiral specifications - tetrahedral chirality is not depicted in the template drawing currently

Rxn ID	Instance	Reaction							Entry Date
		Yield [%]	**Reagent(s)**	**Catalyst(s)**	**Solvent(s)**	**Temp. [C]**	**Time [h]**	**Other**	
3009199	1 of 1	100.0	hydrogen	10 platinum-active carbon	ethyl acetate	unk	8.5	Ambient temperature	2007/11/21

Note: You do not have access to view more than a single precedent for this transformation. If you believe this is in error, please contact ccoley@mit.edu

Reaction IDs corresponding to the 500 highest-yielding examples of this template:

305536, 328791, 345902, 386387, 414788, 420858, 423159, 423917, 425452, 426974, 427061, 427213, 428050, 428329, 428922, 428963, 429345, 429363, 429367, 431565, 432682, 440178, 442950, 444535, 446085, 446365, 446966, 446968, 447723, 448681, 449577, 449964, 626861, 677381, 770139, 770676, 1036445, 1083052, 1089283, 1104649, 1129243, 1154373, 1155190, 1196308, 1375089, 1377787, 1377827, 1378058, 1379364, 1381270, 1383048, 1383051, 1383054, 1383057, 1383058, 1384610, 2193282, 2193333, 2196967, 2308338, 2312535, 2489256, 2510361, 2656682, 2668366, 2668367, 2670806, 2670807, 2733415, 2737785, 2739844, 2843112, 2919897, 2919899, 2984267, 3009199, 3009897, 3023125, 3044308, 3044309, 3047222, 3057463, 3057464, 3060751, 3060752, 3085599, 3086569, 3109852, 3122601, 3160033, 3195989, 3246103, 3253534, 3266404, 3271512, 3283156, 3453693, 3463100, 3478923, 3481465, 3509292, 3564698, 3564874, 3600578, 3600579, 3600580, 3606091, 3607999, 3608001, 3608004, 3618091, 3621235, 3636698, 3686169, 3701861, 4004950, 4058234, 4129483, 4173229, 4216286, 4217836, 4218009, 4218410, 4218411, 4220901, 4221785, 4222193, 4223905, 4225018, 4225019, 4232672, 4232745, 4234718, 4235303, 4236252, 4267783, 4306967, 4325644, 4326521, 4327243, 4396696, 4407615, 4619421, 5355374, 7242847, 7987830, 7991887, 7992329, 8065846, 8101342, 8103090, 8103091, 8103094, 8103095, 8103098, 8104082, 8109037, 8109058, 8753641, 8978845, 9052520, 9052521, 9052522, 9052523, 9427628, 9483277, 9623340, 9629360, 9758574, 9758829, 9838383, 9838384, 9918310, 9921335, 9929356, 9929722, 10095700, 10098856, 10099268, 10367096, 11079506, 11132920, 11266271, 11266274, 22827103, 23679600, 24292299, 27984820, 28226370, 28809905, 29373414, 29424204, 29794697, 30958097, 31045666, 31053148, 31768447, 31768490, 32739349, 33172163, 33975366, 34096920, 35035122, 35519856, 36256633, 36914006, 38753197, 38753240, 39989473, 41238989, 41524051, 43075505, 43451724, 43520402, 43520403, 43721708, 44714201



Template 59c5120405581eb9f575aa9f

Template: `[C:1]-[CH;@@;D3;+0:2](-[C;D1;H3:3])-[CH2;D2;+0:4]-[C:5]=[O;D1;H0:6]>>[C:1]-[C;H0;D3;+0:2](-[C;D1;H3:3])=[CH;D2;+0:4]-[C:5]=[O;D1;H0:6]`

119 total references

Export Reaxys query for precedents

Note: this template should be used for intramolecular reactions ***only***

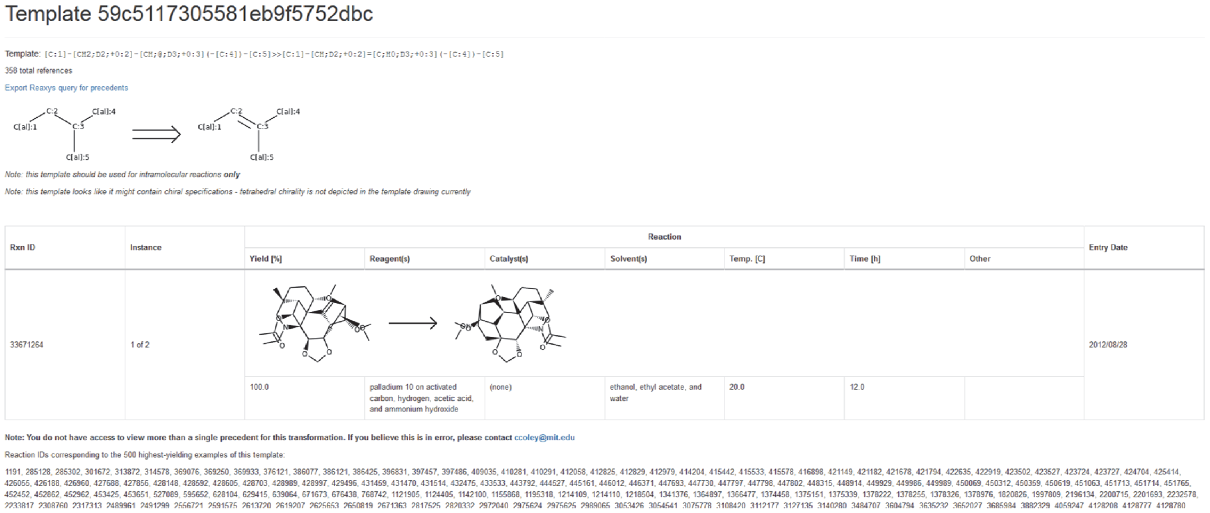
Note: this template looks like it might contain chiral specifications - tetrahedral chirality is not depicted in the template drawing currently

Rxn ID	Instance	Reaction							Entry Date
		Yield [%]	**Reagent(s)**	**Catalyst(s)**	**Solvent(s)**	**Temp. [C]**	**Time [h]**	**Other**	
116086	1 of 12	100.0	palladium 10 on activated carbon and hydrogen	(none)	isopropyl alcohol	unk	2.0		2016/01/12

Note: You do not have access to view more than a single precedent for this transformation. If you believe this is in error, please contact ccoley@mit.edu

Reaction IDs corresponding to the 500 highest-yielding examples of this template:

116086, 200943, 305519, 332553, 416612, 1089278, 1089308, 1095813, 1116434, 1192283, 1344774, 1373437, 1379952, 2032044, 2032223, 2032879, 2318724, 2451080, 2516258, 2548998, 2591031, 2591047, 2601120, 2658575, 2801004, 2834324, 2919892, 2953867, 3039830, 3094007, 3094811, 3113460, 3117768, 3129865, 3390160, 3601881, 3642534, 3667273, 3672842, 4227841, 4236685, 4236874, 4314673, 4315463, 4406015, 4486538, 4499041, 4540359, 4915300, 5164726, 7245635, 7247100, 8716448, 8751089, 8961683, 9040046, 9072373, 9189881, 9407626, 9512231, 9821178, 9908044, 11165888, 24289030, 24291697, 24291703, 29270942, 29699512, 30073530, 31137376, 31762018, 35520148, 36821720, 38066487, 38919325, 42279139



Template 59c5117305581eb9f5752dbc

Template: `[C:1]-[CH2;D2;+0:2]-[CH;@;D3;+0:3](-[C:4])-[C:5]>>[C:1]-[CH;D2;+0:2]=[C;H0;D3;+0:3](-[C:4])-[C:5]`

358 total references

Export Reaxys query for precedents

Note: this template should be used for intramolecular reactions ***only***

Note: this template looks like it might contain chiral specifications - tetrahedral chirality is not depicted in the template drawing currently

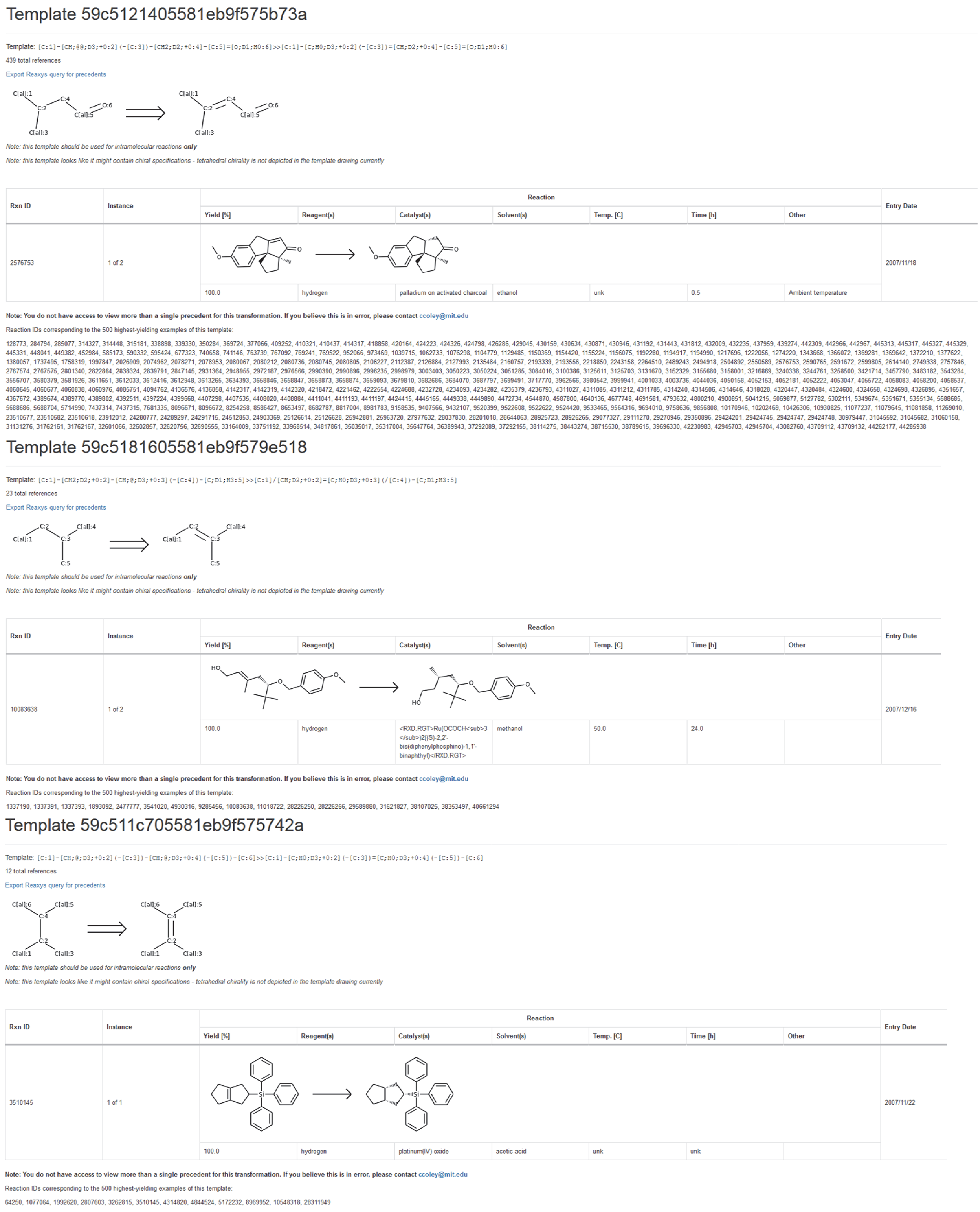
Rxn ID	Instance	Reaction							Entry Date
		Yield [%]	**Reagent(s)**	**Catalyst(s)**	**Solvent(s)**	**Temp. [C]**	**Time [h]**	**Other**	
33671264	1 of 2	100.0	palladium 10 on activated carbon, hydrogen, acetic acid, and ammonium hydroxide	(none)	ethanol, ethyl acetate, and water	20.0	12.0		2012/08/28

Note: You do not have access to view more than a single precedent for this transformation. If you believe this is in error, please contact ccoley@mit.edu

Reaction IDs corresponding to the 500 highest-yielding examples of this template:

1191, 285128, 285302, 301672, 313872, 314578, 369076, 369250, 369933, 376121, 386077, 386121, 386425, 396831, 397457, 397486, 409035, 410281, 410291, 412058, 412825, 412829, 412979, 414204, 415442, 415533, 415578, 416898, 421149, 421182, 421678, 421794, 422635, 422919, 423502, 423527, 423724, 423727, 424704, 425414, 426055, 426188, 426960, 427688, 427856, 428148, 428592, 428605, 428703, 428989, 428997, 429496, 431459, 431470, 431514, 432475, 433533, 443792, 444527, 445161, 446012, 446371, 447693, 447730, 447797, 447798, 447802, 448315, 448914, 449929, 449986, 449989, 450069, 450312, 450359, 450619, 451063, 451713, 451714, 451765, 452452, 452862, 452962, 453425, 453651, 527089, 595652, 628104, 629415, 639064, 671673, 676438, 768742, 1121905, 1124405, 1142100, 1155868, 1195318, 1214109, 1214110, 1218504, 1341376, 1364897, 1366477, 1374458, 1375151, 1375339, 1378222, 1378255, 1378326, 1378976, 1820826, 1997809, 2196134, 2200715, 2201693, 2232578, 2233817, 2308760, 2317313, 2489961, 2491299, 2556721, 2591575, 2613720, 2619207, 2625653, 2650819, 2671363, 2817525, 2820332, 2972040, 2975624, 2975625, 2989065, 3053426, 3054541, 3075778, 3108420, 3112177, 3127135, 3140280, 3484707, 3604794, 3635232, 3652027, 3685984, 3882329, 4059247, 4128208, 4128777, 4128780

Figure S19. Reaction templates extracted from substrate-controlled reductions of alkenes. None of the 14 templates (with the remaining ones shown in **Figures S20-S22**) used to generate precursors for the chiral cyclopentanone from **Figure S15** accounts for necessary substituents dictating the reaction's stereoselective outcome.



Template 59c5121405581eb9f575b73a

Template: `[C:1]-[CH;@@;D3;+0:2](-[C:3])-[CH2;D2;+0:4]-[C:5]=[O;D1;H0:6]>>[C:1]-[C;H0;D3;+0:2](-[C:3])=[CH;D2;+0:4]-[C:5]=[O;D1;H0:6]`

439 total references

Export Reaxys query for precedents

Note: this template should be used for intramolecular reactions ***only***

Note: this template looks like it might contain chiral specifications - tetrahedral chirality is not depicted in the template drawing currently

Rxn ID	Instance	Reaction							Entry Date
		Yield [%]	Reagent(s)	Catalyst(s)	Solvent(s)	Temp. [C]	Time [h]	Other	
2576753	1 of 2	100.0	hydrogen	palladium on activated charcoal	ethanol	unk	0.5	Ambient temperature	2007/11/18

Note: You do not have access to view more than a single precedent for this transformation. If you believe this is in error, please contact ccoley@mit.edu

Reaction IDs corresponding to the 500 highest-yielding examples of this template:

128773, 284794, 285077, 314327, 314448, 315181, 338898, 339330, 350284, 369724, 377066, 409252, 410321, 410437, 414317, 418858, 420164, 424223, 424326, 424798, 426286, 429045, 430159, 430634, 430871, 430946, 431192, 431443, 431812, 432009, 432235, 437959, 439274, 442309, 442966, 442967, 445313, 445317, 445327, 445329, 445331, 448041, 449382, 452984, 585173, 590332, 595424, 677323, 740658, 741146, 763739, 767092, 769241, 769522, 952066, 973469, 1039715, 1062733, 1076298, 1104779, 1129485, 1150369, 1154420, 1155224, 1156075, 1192280, 1194917, 1194990, 1217696, 1222056, 1274220, 1343668, 1366072, 1369281, 1369642, 1372210, 1377622, 1380057, 1737495, 1758319, 1997847, 2026909, 2074962, 2078271, 2078953, 2080067, 2080212, 2080736, 2080745, 2080805, 2106227, 2112387, 2126884, 2127993, 2135484, 2160757, 2193339, 2193556, 2218850, 2243158, 2264510, 2489243, 2494918, 2504892, 2550589, 2576753, 2590765, 2591672, 2599805, 2614140, 2749338, 2757846, 2767574, 2767575, 2801340, 2822864, 2838324, 2839791, 2847145, 2931364, 2948955, 2972187, 2976566, 2990390, 2990896, 2996235, 2998979, 3003403, 3050223, 3050224, 3051285, 3084016, 3100386, 3125611, 3125703, 3131670, 3152329, 3155680, 3158001, 3216869, 3240338, 3244761, 3258500, 3421714, 3457790, 3483182, 3543284, 3556707, 3580379, 3581926, 3611651, 3612033, 3612416, 3612948, 3613265, 3634393, 3658846, 3658847, 3658873, 3658874, 3659093, 3679810, 3682686, 3684070, 3687797, 3699491, 3717770, 3962566, 3980542, 3999941, 4001033, 4003736, 4044036, 4050158, 4052153, 4052181, 4052222, 4053047, 4055722, 4058083, 4058200, 4058537, 4060645, 4060677, 4060838, 4060976, 4085751, 4094762, 4136576, 4136858, 4142317, 4142319, 4142320, 4218472, 4221462, 4222554, 4224688, 4232728, 4234093, 4234282, 4235379, 4236793, 4311027, 4311085, 4311212, 4311785, 4314240, 4314506, 4314646, 4318028, 4320447, 4320484, 4324600, 4324658, 4324698, 4326895, 4351657, 4367672, 4389674, 4389770, 4389802, 4392511, 4397224, 4399668, 4407298, 4407535, 4408020, 4408884, 4411041, 4411193, 4411197, 4424415, 4445165, 4449338, 4449890, 4472734, 4544870, 4587800, 4640136, 4677748, 4691581, 4793632, 4800210, 4900851, 5041215, 5069877, 5127782, 5302111, 5349674, 5351671, 5355134, 5688685, 5688686, 5688704, 5714990, 7437314, 7437315, 7681335, 8096671, 8096672, 8254258, 8586427, 8653497, 8682787, 8817004, 8981783, 9158535, 9407566, 9432107, 9520399, 9522608, 9522622, 9524420, 9533465, 9564316, 9694010, 9758636, 9856808, 10170946, 10202469, 10426306, 10930825, 11077237, 11079645, 11081858, 11269010, 23510577, 23510582, 23510618, 23912012, 24280777, 24289297, 24291715, 24512853, 24903369, 25126614, 25126628, 25942881, 25963720, 27977632, 28037830, 28201018, 28644063, 28925723, 28926265, 29077327, 29111270, 29270946, 29350896, 29424201, 29424745, 29424747, 29424748, 30979447, 31045592, 31045682, 31060158, 31131276, 31762161, 31762167, 32601066, 32602857, 32620756, 32690555, 33164009, 33751192, 33968514, 34817861, 35035017, 35317004, 35647764, 36389943, 37292089, 37292155, 38114275, 38443274, 38715530, 38789615, 39696330, 42230983, 42945703, 42945704, 43082760, 43709112, 43709132, 44262177, 44285938

Template 59c5181605581eb9f579e518

Template: `[C:1]-[CH2;D2;+0:2]-[CH;@;D3;+0:3](-[C:4])-[C;D1;H3:5]>>[C:1]/[CH;D2;+0:2]=[C;H0;D3;+0:3](/[C:4])-[C;D1;H3:5]`

23 total references

Export Reaxys query for precedents

Note: this template should be used for intramolecular reactions ***only***

Note: this template looks like it might contain chiral specifications - tetrahedral chirality is not depicted in the template drawing currently

Rxn ID	Instance	Reaction							Entry Date
		Yield [%]	Reagent(s)	Catalyst(s)	Solvent(s)	Temp. [C]	Time [h]	Other	
10083638	1 of 2	100.0	hydrogen	<RXD.RGT>Ru(OCOCH₃)2((S)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)</RXD.RGT>	methanol	50.0	24.0		2007/12/16

Note: You do not have access to view more than a single precedent for this transformation. If you believe this is in error, please contact ccoley@mit.edu

Reaction IDs corresponding to the 500 highest-yielding examples of this template:

1337190, 1337391, 1337393, 1893092, 2477777, 3541020, 4930316, 9285456, 10083638, 11018722, 28226250, 28226266, 29589880, 31621827, 38107025, 38353497, 40661294

Template 59c511c705581eb9f575742a

Template: `[C:1]-[CH;@;D3;+0:2](-[C:3])-[CH;@;D3;+0:4](-[C:5])-[C:6]>>[C:1]-[C;H0;D3;+0:2](-[C:3])=[C;H0;D3;+0:4](-[C:5])-[C:6]`

12 total references

Export Reaxys query for precedents

Note: this template should be used for intramolecular reactions ***only***

Note: this template looks like it might contain chiral specifications - tetrahedral chirality is not depicted in the template drawing currently

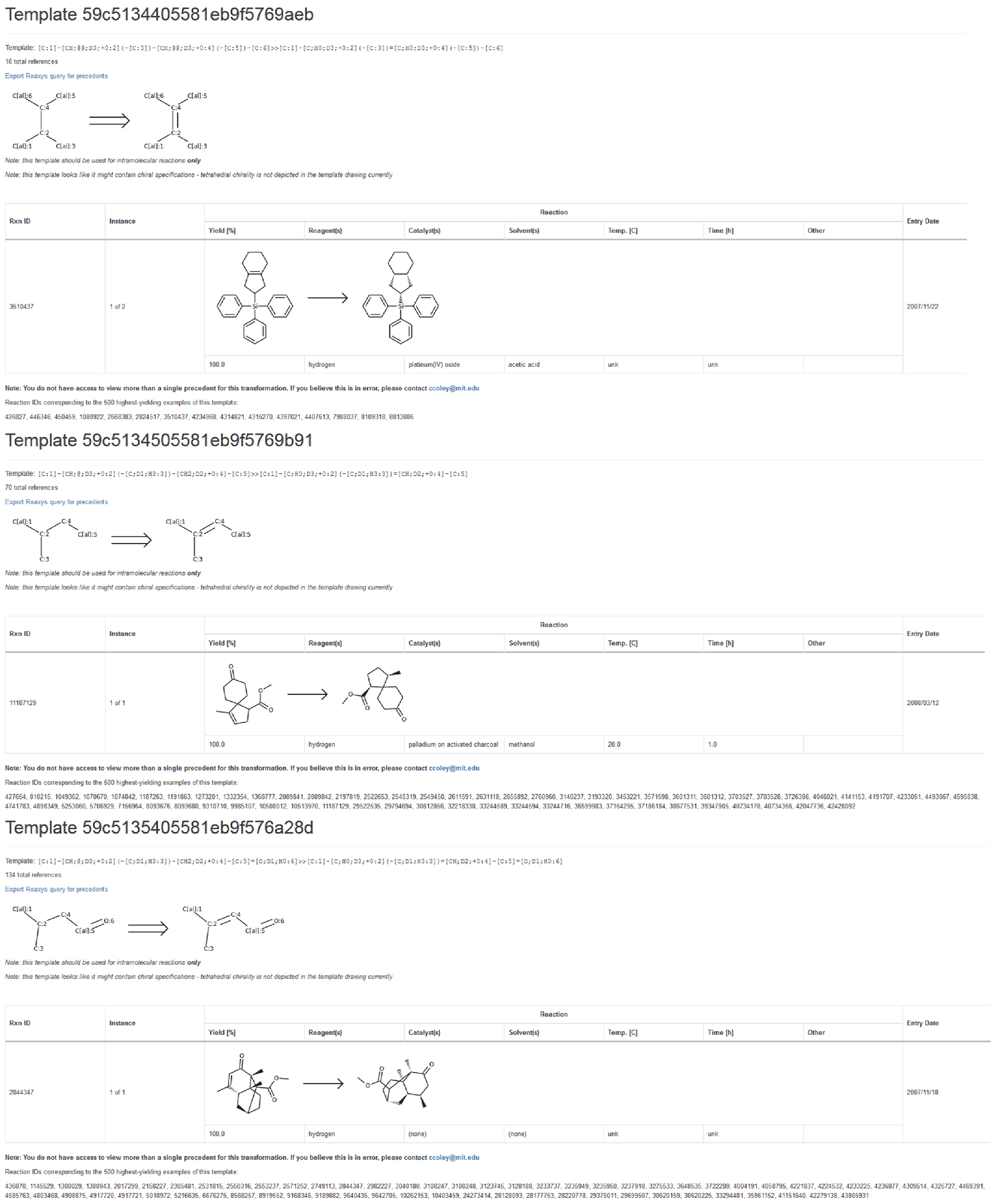
Rxn ID	Instance	Reaction							Entry Date
		Yield [%]	Reagent(s)	Catalyst(s)	Solvent(s)	Temp. [C]	Time [h]	Other	
3510145	1 of 1	100.0	hydrogen	platinum(IV) oxide	acetic acid	unk	unk		2007/11/22

Note: You do not have access to view more than a single precedent for this transformation. If you believe this is in error, please contact ccoley@mit.edu

Reaction IDs corresponding to the 500 highest-yielding examples of this template:

64250, 1077064, 1992620, 2807603, 3262815, 3510145, 4314820, 4844524, 5172232, 8969952, 10548318, 28311949

Figure S20. Reaction templates extracted from substrate-controlled reductions of alkenes. None of the 14 templates (with the remaining ones shown in **Figures S21-S22**) used to generate precursors for the chiral cyclopentanone from **Figure S15** accounts for necessary substituents dictating the reaction's stereoselective outcome.



Template 59c5134405581eb9f5769aeb

Template: `[C:1]-[CH;@@;D3;+0:2](-[C:3])-[CH;@@;D3;+0:4](-[C:5])-[C:6]>>[C:1]-[C;H0;D3;+0:2](-[C:3])=[C;H0;D3;+0:4](-[C:5])-[C:6]`

16 total references

Export Reaxys query for precedents

Note: this template should be used for intramolecular reactions ***only***

Note: this template looks like it might contain chiral specifications - tetrahedral chirality is not depicted in the template drawing currently

Rxn ID	**Instance**	**Reaction**							**Entry Date**
		Yield [%]	**Reagent(s)**	**Catalyst(s)**	**Solvent(s)**	**Temp. [C]**	**Time [h]**	**Other**	
3510437	1 of 2	100.0	hydrogen	platinum(IV) oxide	acetic acid	unk	unk		2007/11/22

Note: You do not have access to view more than a single precedent for this transformation. If you believe this is in error, please contact ccoley@mit.edu

Reaction IDs corresponding to the 500 highest-yielding examples of this template:

426827, 446346, 450459, 1080922, 2668383, 2824517, 3510437, 4234968, 4314821, 4315270, 4397021, 4407613, 7988037, 8109318, 8813886

Template 59c5134505581eb9f5769b91

Template: `[C:1]-[CH;@;D3;+0:2](-[C;D1;H3:3])-[CH2;D2;+0:4]-[C:5]>>[C:1]-[C;H0;D3;+0:2](-[C;D1;H3:3])=[CH;D2;+0:4]-[C:5]`

70 total references

Export Reaxys query for precedents

Note: this template should be used for intramolecular reactions ***only***

Note: this template looks like it might contain chiral specifications - tetrahedral chirality is not depicted in the template drawing currently

Rxn ID	**Instance**	**Reaction**							**Entry Date**
		Yield [%]	**Reagent(s)**	**Catalyst(s)**	**Solvent(s)**	**Temp. [C]**	**Time [h]**	**Other**	
11187129	1 of 1	100.0	hydrogen	palladium on activated charcoal	methanol	20.0	1.0		2008/03/12

Note: You do not have access to view more than a single precedent for this transformation. If you believe this is in error, please contact ccoley@mit.edu

Reaction IDs corresponding to the 500 highest-yielding examples of this template:

427654, 810215, 1049362, 1070670, 1074842, 1187263, 1191863, 1273201, 1332354, 1368777, 2009841, 2009842, 2197819, 2522653, 2545319, 2549450, 2611591, 2631118, 2655892, 2760960, 3140237, 3193320, 3453221, 3571598, 3601311, 3601312, 3703527, 3703528, 3726386, 4046021, 4141153, 4191707, 4233051, 4493067, 4595838, 4741783, 4898349, 5253060, 5706929, 7156964, 8093676, 8093680, 9310710, 9985107, 10508012, 10513970, 11187129, 29522535, 29794694, 30812856, 32218338, 33244589, 33244594, 33244716, 36599983, 37164295, 37186184, 38677531, 39347905, 40734178, 40734366, 42047736, 42428092

Template 59c5135405581eb9f576a28d

Template: `[C:1]-[CH;@;D3;+0:2](-[C;D1;H3:3])-[CH2;D2;+0:4]-[C:5]=[O;D1;H0:6]>>[C:1]-[C;H0;D3;+0:2](-[C;D1;H3:3])=[CH;D2;+0:4]-[C:5]=[O;D1;H0:6]`

134 total references

Export Reaxys query for precedents

Note: this template should be used for intramolecular reactions ***only***

Note: this template looks like it might contain chiral specifications - tetrahedral chirality is not depicted in the template drawing currently

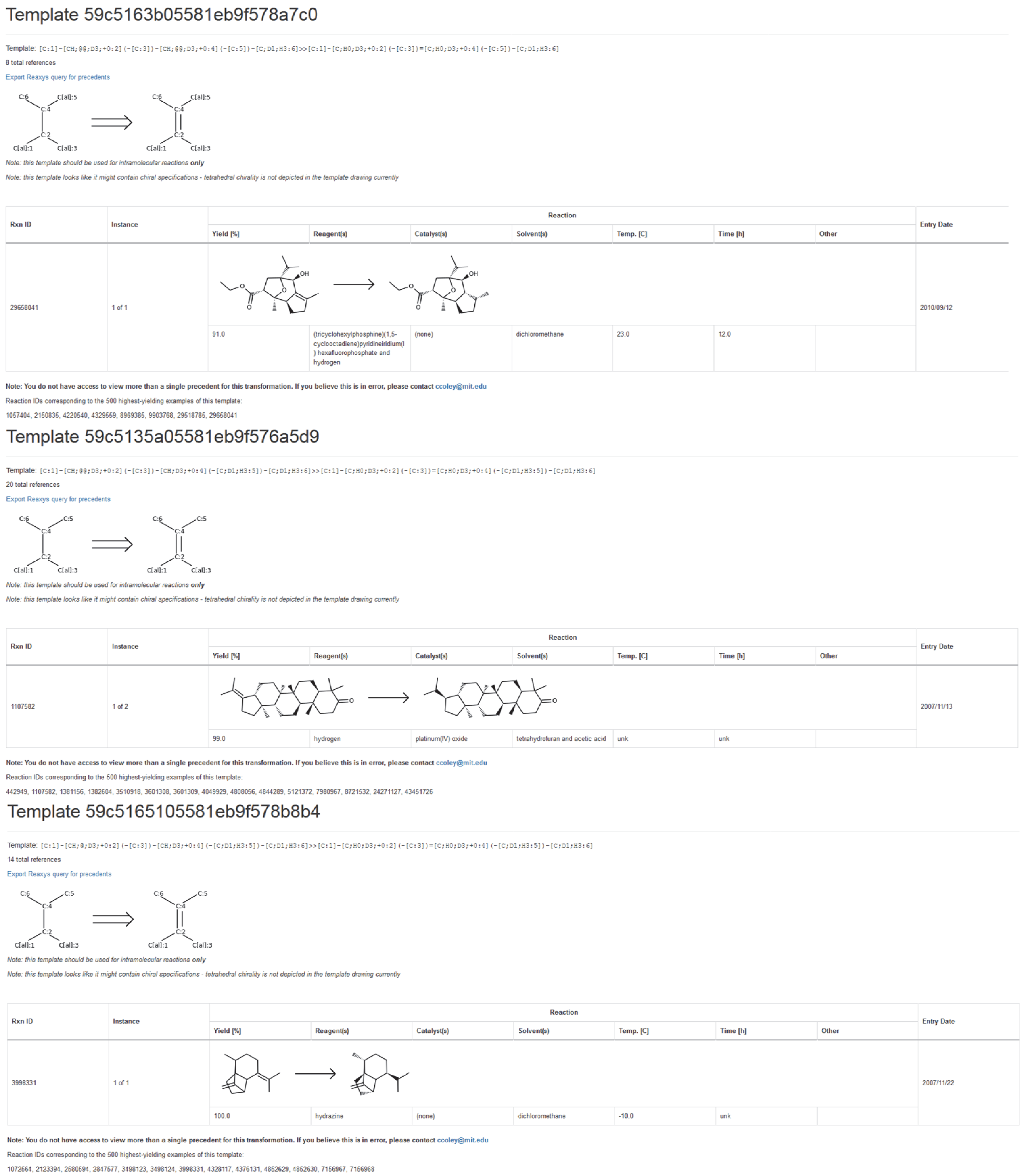
Rxn ID	**Instance**	**Reaction**							**Entry Date**
		Yield [%]	**Reagent(s)**	**Catalyst(s)**	**Solvent(s)**	**Temp. [C]**	**Time [h]**	**Other**	
2844347	1 of 1	100.0	hydrogen	(none)	(none)	unk	unk		2007/11/18

Note: You do not have access to view more than a single precedent for this transformation. If you believe this is in error, please contact ccoley@mit.edu

Reaction IDs corresponding to the 500 highest-yielding examples of this template:

436870, 1145529, 1380029, 1380943, 2017299, 2158227, 2305481, 2531815, 2550316, 2553237, 2571252, 2749113, 2844347, 2982227, 3040180, 3108247, 3108248, 3123745, 3128188, 3233737, 3235949, 3235950, 3237910, 3275533, 3648535, 3722289, 4004191, 4058795, 4221837, 4224532, 4233225, 4236877, 4309514, 4325727, 4469391, 4585763, 4803468, 4908875, 4917720, 4917721, 5018972, 5216635, 6676275, 8568257, 8919552, 9168346, 9189882, 9640435, 9642705, 10262153, 10403459, 24273414, 28128093, 28177753, 28220778, 29375011, 29699507, 30620159, 30620225, 33294481, 35961152, 41151640, 42279138, 43805931

Figure S21. Reaction templates extracted from substrate-controlled reductions of alkenes. None of the 14 templates (with the remaining ones shown in **Figure S22**) used to generate precursors for the chiral cyclopentanone from **Figure S15** accounts for necessary substituents dictating the reaction's stereoselective outcome.



Template 59c5163b05581eb9f578a7c0

Template: `[C:1]-[CH;@@;D3;+0:2](-[C:3])-[CH;@@;D3;+0:4](-[C:5])-[C;D1;H3:6]>>[C:1]-[C;H0;D3;+0:2](-[C:3])=[C;H0;D3;+0:4](-[C:5])-[C;D1;H3:6]`

8 total references

Export Reaxys query for precedents

Note: this template should be used for intramolecular reactions ***only***

Note: this template looks like it might contain chiral specifications - tetrahedral chirality is not depicted in the template drawing currently

Rxn ID	Instance	Reaction							Entry Date
		Yield [%]	Reagent(s)	Catalyst(s)	Solvent(s)	Temp. [C]	Time [h]	Other	
29658041	1 of 1	91.0	(tricyclohexylphosphine)(1,5-cyclooctadiene)pyridineiridium(I) hexafluorophosphate and hydrogen	(none)	dichloromethane	23.0	12.0		2010/09/12

Note: You do not have access to view more than a single precedent for this transformation. If you believe this is in error, please contact ccoley@mit.edu

Reaction IDs corresponding to the 500 highest-yielding examples of this template:

1057404, 2150835, 4220540, 4329559, 8969385, 9903768, 29518785, 29658041

Template 59c5135a05581eb9f576a5d9

Template: `[C:1]-[CH;@@;D3;+0:2](-[C:3])-[CH;D3;+0:4](-[C;D1;H3:5])-[C;D1;H3:6]>>[C:1]-[C;H0;D3;+0:2](-[C:3])=[C;H0;D3;+0:4](-[C;D1;H3:5])-[C;D1;H3:6]`

20 total references

Export Reaxys query for precedents

Note: this template should be used for intramolecular reactions ***only***

Note: this template looks like it might contain chiral specifications - tetrahedral chirality is not depicted in the template drawing currently

Rxn ID	Instance	Reaction							Entry Date
		Yield [%]	Reagent(s)	Catalyst(s)	Solvent(s)	Temp. [C]	Time [h]	Other	
1107582	1 of 2	99.0	hydrogen	platinum(IV) oxide	tetrahydrofuran and acetic acid	unk	unk		2007/11/13

Note: You do not have access to view more than a single precedent for this transformation. If you believe this is in error, please contact ccoley@mit.edu

Reaction IDs corresponding to the 500 highest-yielding examples of this template:

442949, 1107582, 1381156, 1382604, 3510918, 3601308, 3601309, 4049929, 4808056, 4844289, 5121372, 7980967, 8721532, 24271127, 43451726

Template 59c5165105581eb9f578b8b4

Template: `[C:1]-[CH;@;D3;+0:2](-[C:3])-[CH;D3;+0:4](-[C;D1;H3:5])-[C;D1;H3:6]>>[C:1]-[C;H0;D3;+0:2](-[C:3])=[C;H0;D3;+0:4](-[C;D1;H3:5])-[C;D1;H3:6]`

14 total references

Export Reaxys query for precedents

Note: this template should be used for intramolecular reactions ***only***

Note: this template looks like it might contain chiral specifications - tetrahedral chirality is not depicted in the template drawing currently

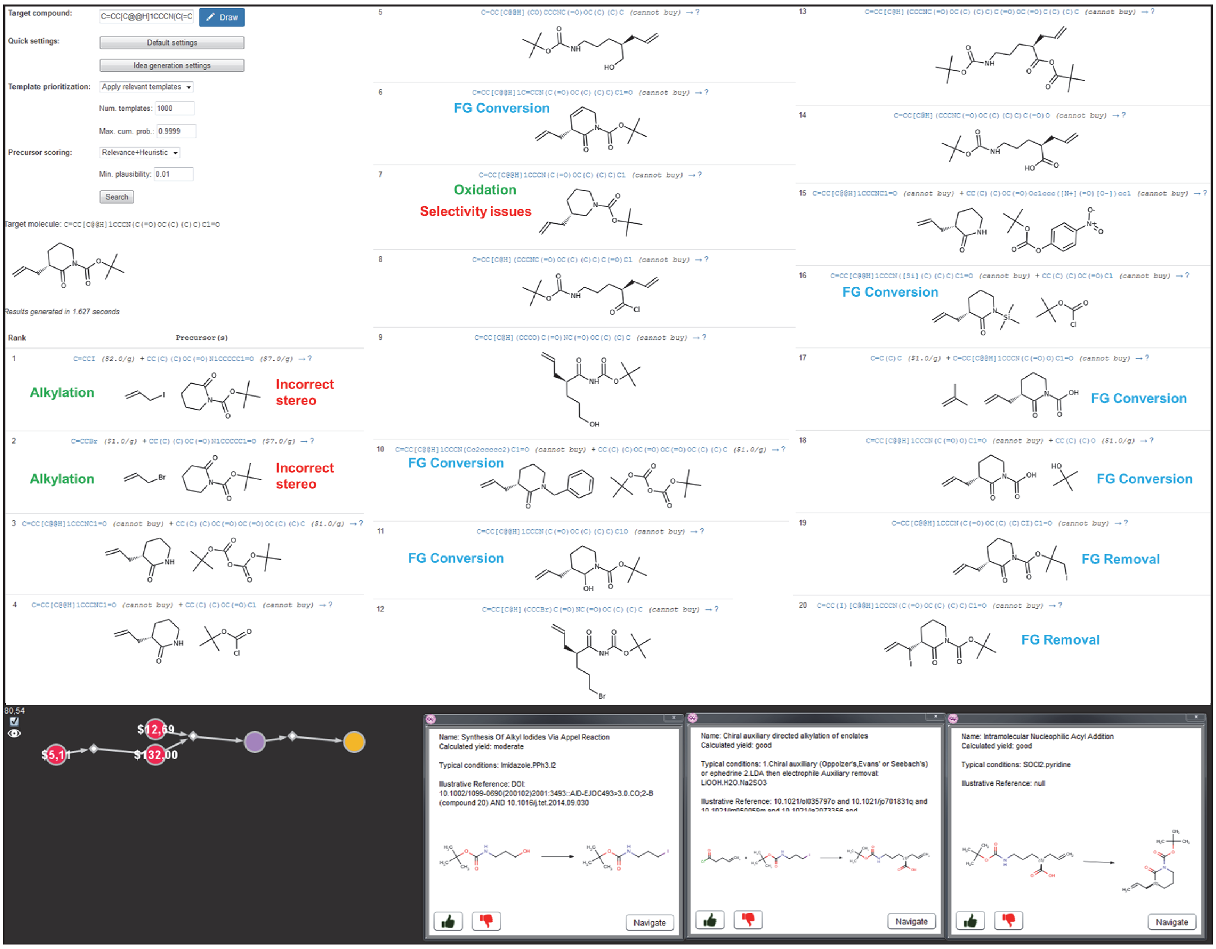
Rxn ID	Instance	Reaction							Entry Date
		Yield [%]	Reagent(s)	Catalyst(s)	Solvent(s)	Temp. [C]	Time [h]	Other	
3998331	1 of 1	100.0	hydrazine	(none)	dichloromethane	-10.0	unk		2007/11/22

Note: You do not have access to view more than a single precedent for this transformation. If you believe this is in error, please contact ccoley@mit.edu

Reaction IDs corresponding to the 500 highest-yielding examples of this template:

1072564, 2123394, 2580594, 2847577, 3498123, 3498124, 3998331, 4328117, 4376131, 4852629, 4852630, 7156967, 7156968

Figure S22. Reaction templates extracted from substrate-controlled reductions of alkenes. None of the 14 templates used to generate precursors for the chiral cyclopentanone from **Figure S15** accounts for necessary substituents dictating reaction's stereoselective outcome.



Target compound: C=CC[C@@H]1CCCN(C(=C

Quick settings:

Template prioritization: Apply relevant templates

Num. templates: 1000

Max. cum. prob.: 0.9999

Precursor scoring: Relevance+Heuristic

Min. plausibility: 0.01

Target molecule: C=CC[C@@H]1CCCN(C(=O)OC(C)(C)C)C1=O

Results generated in 1.627 seconds

Rank	Precursor(s)
1	C=CCI *($2.0/g)* + CC(C)(C)OC(=O)N1CCCCC1=O *($7.0/g)* → ?
2	C=CCBr *($1.0/g)* + CC(C)(C)OC(=O)N1CCCCC1=O *($7.0/g)* → ?
3	C=CC[C@@H]1CCCNC1=O *(cannot buy)* + CC(C)(C)OC(=O)OC(=O)OC(C)(C)C *($1.0/g)* → ?
4	C=CC[C@@H]1CCCNC1=O *(cannot buy)* + CC(C)(C)OC(=O)Cl *(cannot buy)* → ?
5	C=CC[C@@H](CO)CCCNC(=O)OC(C)(C)C *(cannot buy)* → ?
6	C=CC[C@@H]1C=CCN(C(=O)OC(C)(C)C)C1=O *(cannot buy)* → ?
7	C=CC[C@@H]1CCCN(C(=O)OC(C)(C)C)C1 *(cannot buy)* → ?
8	C=CC[C@H](CCCNC(=O)OC(C)(C)C)C(=O)Cl *(cannot buy)* → ?
9	C=CC[C@H](CCCO)C(=O)NC(=O)OC(C)(C)C *(cannot buy)* → ?
10	C=CC[C@@H]1CCCN(Cc2ccccc2)C1=O *(cannot buy)* + CC(C)(C)OC(=O)OC(=O)OC(C)(C)C *($1.0/g)* → ?
11	C=CC[C@@H]1CCCN(C(=O)OC(C)(C)C)C1O *(cannot buy)* → ?
12	C=CC[C@H](CCCBr)C(=O)NC(=O)OC(C)(C)C *(cannot buy)* → ?
13	C=CC[C@H](CCCNC(=O)OC(C)(C)C)C(=O)OC(=O)C(C)(C)C *(cannot buy)* → ?
14	C=CC[C@H](CCCNC(=O)OC(C)(C)C)C(=O)O *(cannot buy)* → ?
15	C=CC[C@@H]1CCCNC1=O *(cannot buy)* + CC(C)(C)OC(=O)Oc1ccc([N+](=O)[O-])cc1 *(cannot buy)* → ?
16	C=CC[C@@H]1CCCN([Si](C)(C)C)C1=O *(cannot buy)* + CC(C)(C)OC(=O)Cl *(cannot buy)* → ?
17	C=C(C)C *($1.0/g)* + C=CC[C@@H]1CCCN(C(=O)O)C1=O *(cannot buy)* → ?
18	C=CC[C@@H]1CCCN(C(=O)O)C1=O *(cannot buy)* + CC(C)(C)O *($1.0/g)* → ?
19	C=CC[C@@H]1CCCN(C(=O)OC(C)(C)CI)C1=O *(cannot buy)* → ?
20	C=CC(I)[C@@H]1CCCN(C(=O)OC(C)(C)C)C1=O *(cannot buy)* → ?

Name: Synthesis Of Alkyl Iodides Via Appel Reaction
Calculated yield: moderate

Typical conditions: Imidazole.PPh3.I2

Illustrative Reference: DOI: 10.1002/1099-0690(200102)2001:3493::AID-EJOC493>3.0.CO;2-B (compound 20) AND 10.1016/j.tet.2014.09.030

Name: Chiral auxiliary directed alkylation of enolates
Calculated yield: good

Typical conditions: 1.Chiral auxilliary (Oppolzer's,Evans' or Seebach's) or ephedrine 2.LDA then electrophile Auxiliary removal: LiOOH.H2O.Na2SO3

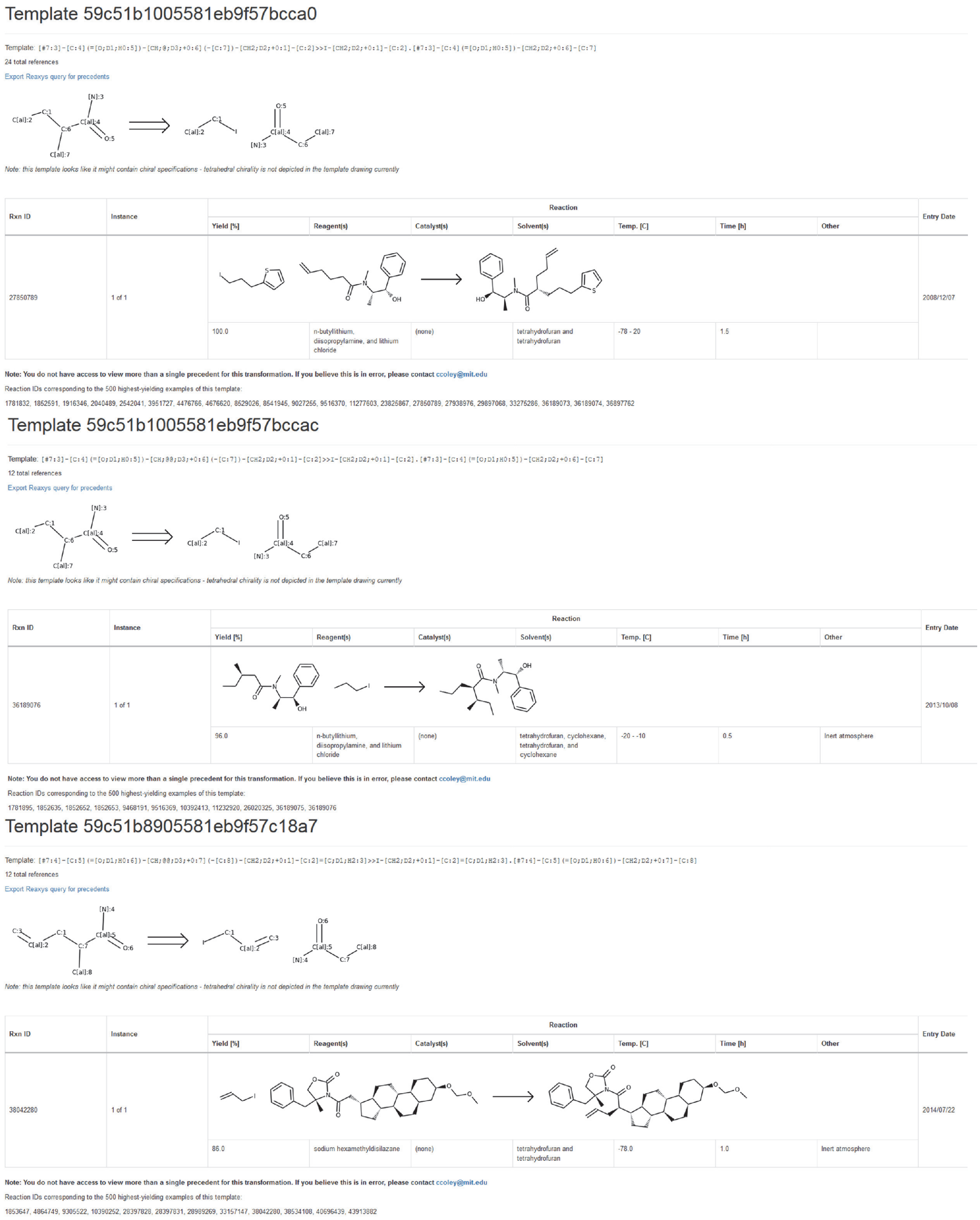
Illustrative Reference: 10.1021/ol035797o and 10.1021/jo701831q and 10.1021/jm050059m and 10.1021/ja2073356 and

Name: Intramolecular Nucleophilic Acyl Addition
Calculated yield: good

Typical conditions: SOCl2.pyridine

Illustrative Reference: null

Figure S23. Retrosynthetic planning of a chiral lactam in MIT's ASKCOS system. Templates of stereoselective alkylations of the lactam (see **Figure S24**) do not account for necessary structural features dictating the reaction's stereoselective outcome. Bottom: In contrast, in Chematica's solution, the necessary stereocenter is created in acyclic system via alkylation controlled by a chiral auxiliary (cf. typical conditions for the second step). Subsequent removal of the auxiliary and intramolecular acylation yield the target molecule.



Template 59c51b1005581eb9f57bcca0

Template: `[#7:3]-[C:4](=[O;D1;H0:5])-[CH;@;D3;+0:6](-[C:7])-[CH2;D2;+0:1]-[C:2]>>I-[CH2;D2;+0:1]-[C:2].[#7:3]-[C:4](=[O;D1;H0:5])-[CH2;D2;+0:6]-[C:7]`

24 total references

Export Reaxys query for precedents

Note: this template looks like it might contain chiral specifications - tetrahedral chirality is not depicted in the template drawing currently

Rxn ID	Instance	Reaction							Entry Date
		Yield [%]	Reagent(s)	Catalyst(s)	Solvent(s)	Temp. [C]	Time [h]	Other	
27850789	1 of 1	100.0	n-butyllithium, diisopropylamine, and lithium chloride	(none)	tetrahydrofuran and tetrahydrofuran	-78 - 20	1.5		2008/12/07

Note: You do not have access to view more than a single precedent for this transformation. If you believe this is in error, please contact ccoley@mit.edu

Reaction IDs corresponding to the 500 highest-yielding examples of this template:

1781832, 1852591, 1916346, 2040489, 2542041, 3951727, 4476766, 4676620, 8529026, 8541945, 9027255, 9516370, 11277603, 23825867, 27850789, 27938976, 29897068, 33275286, 36189073, 36189074, 36897762

Template 59c51b1005581eb9f57bccac

Template: `[#7:3]-[C:4](=[O;D1;H0:5])-[CH;@@;D3;+0:6](-[C:7])-[CH2;D2;+0:1]-[C:2]>>I-[CH2;D2;+0:1]-[C:2].[#7:3]-[C:4](=[O;D1;H0:5])-[CH2;D2;+0:6]-[C:7]`

12 total references

Export Reaxys query for precedents

Note: this template looks like it might contain chiral specifications - tetrahedral chirality is not depicted in the template drawing currently

Rxn ID	Instance	Reaction							Entry Date
		Yield [%]	Reagent(s)	Catalyst(s)	Solvent(s)	Temp. [C]	Time [h]	Other	
36189076	1 of 1	96.0	n-butyllithium, diisopropylamine, and lithium chloride	(none)	tetrahydrofuran, cyclohexane, tetrahydrofuran, and cyclohexane	-20 - -10	0.5	Inert atmosphere	2013/10/08

Note: You do not have access to view more than a single precedent for this transformation. If you believe this is in error, please contact ccoley@mit.edu

Reaction IDs corresponding to the 500 highest-yielding examples of this template:

1781895, 1852635, 1852652, 1852653, 9468191, 9516369, 10392413, 11232920, 26020325, 36189075, 36189076

Template 59c51b8905581eb9f57c18a7

Template: `[#7:4]-[C:5](=[O;D1;H0:6])-[CH;@@;D3;+0:7](-[C:8])-[CH2;D2;+0:1]-[C:2]=[C;D1;H2:3]>>I-[CH2;D2;+0:1]-[C:2]=[C;D1;H2:3].[#7:4]-[C:5](=[O;D1;H0:6])-[CH2;D2;+0:7]-[C:8]`

12 total references

Export Reaxys query for precedents

Note: this template looks like it might contain chiral specifications - tetrahedral chirality is not depicted in the template drawing currently

Rxn ID	Instance	Reaction							Entry Date
		Yield [%]	Reagent(s)	Catalyst(s)	Solvent(s)	Temp. [C]	Time [h]	Other	
38042280	1 of 1	86.0	sodium hexamethyldisilazane	(none)	tetrahydrofuran and tetrahydrofuran	-78.0	1.0	Inert atmosphere	2014/07/22

Note: You do not have access to view more than a single precedent for this transformation. If you believe this is in error, please contact ccoley@mit.edu

Reaction IDs corresponding to the 500 highest-yielding examples of this template:

1853647, 4864749, 9305522, 10390252, 28397828, 28397831, 28989269, 33157147, 38042280, 38534108, 40696439, 43913882

Figure S24. ASKCOS' automatically extracted cores of substrate-controlled alkylation of imides do not account for the necessary structural features controlling the reaction's outcome.

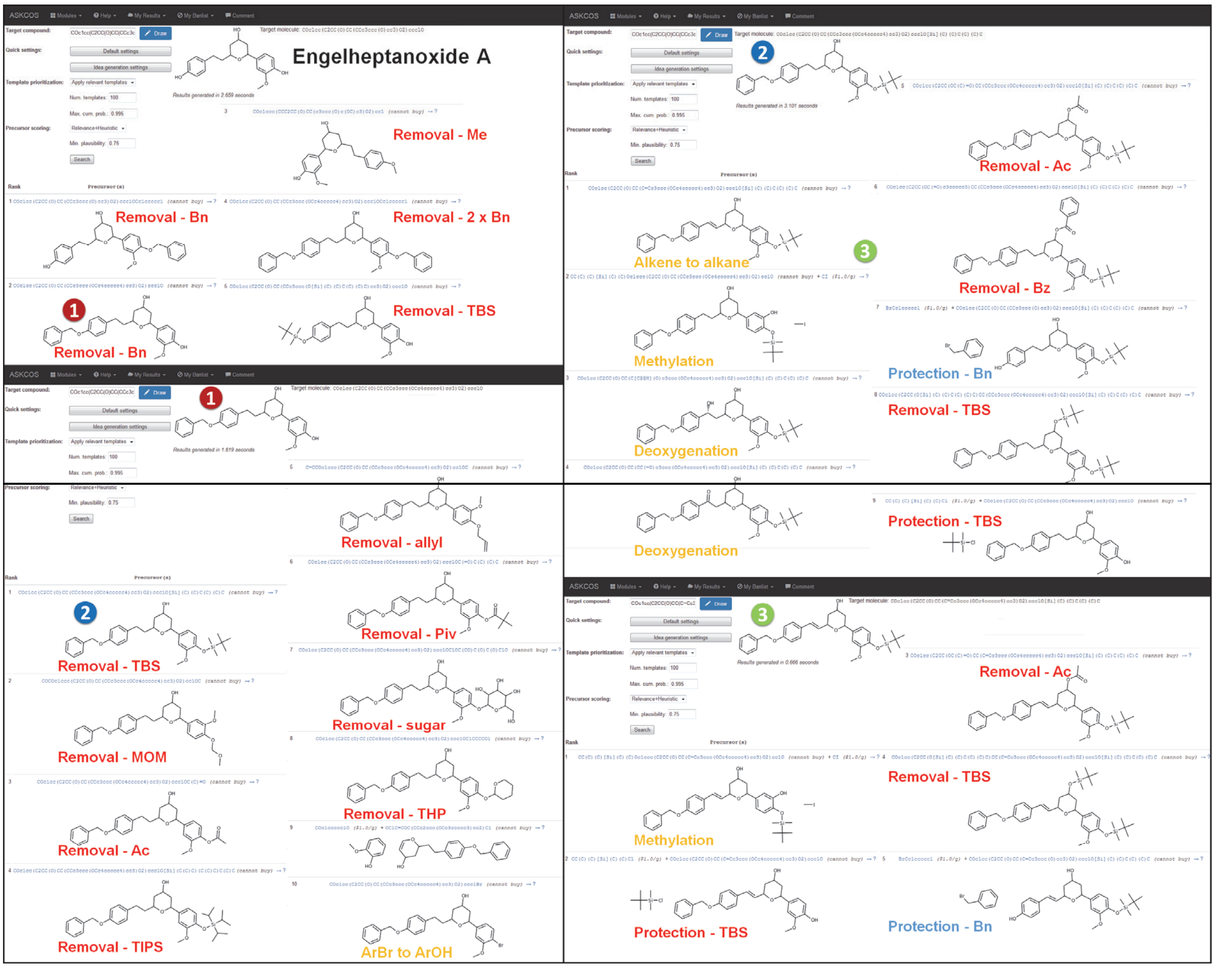


Figure S25. Attempted multistep retrosynthetic planning of Engelheptanoxide A in MIT's ASKCOS system. In this final exercise, we attempted to design a synthetic pathway for Engelheptanoxide A, for which a synthetic plan was previously predicted by the Chematica software and executed experimentally (see *Chem* **4**, 522, **2018**). The suggestions obtained from ASKCOS system for this target molecule and a few proposed predecessors are nonproductive and limited to deprotections, protections, and nonproductive functional group interconversions. None of the proposed disconnections allowed for the formation of the key tetrahydropyran fragment – either via Prins cyclisation utilized previously in the synthesis of this class of compounds or even via a must-know S_N2 alkylation of alcohol. Top left: top 10 out of 88 returned results are shown, bottom left: top 10 out of 47 returned results are shown, top right: top 9 of 37 returned results are shown, bottom right: top 5 out of 30 returned results are shown. Note: The statement that no proper reactions were found pertains to the full sets of results (88/47/37/30), not only the top examples shown.