Recent Advances in IMCRs (Passerini and Ugi Reactions)

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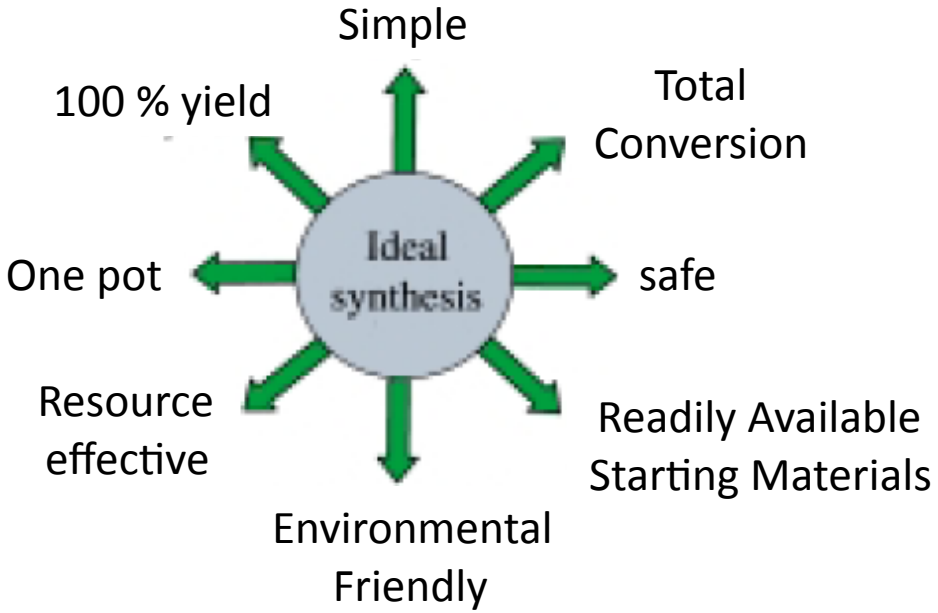
Group Meeting

May 16,2008

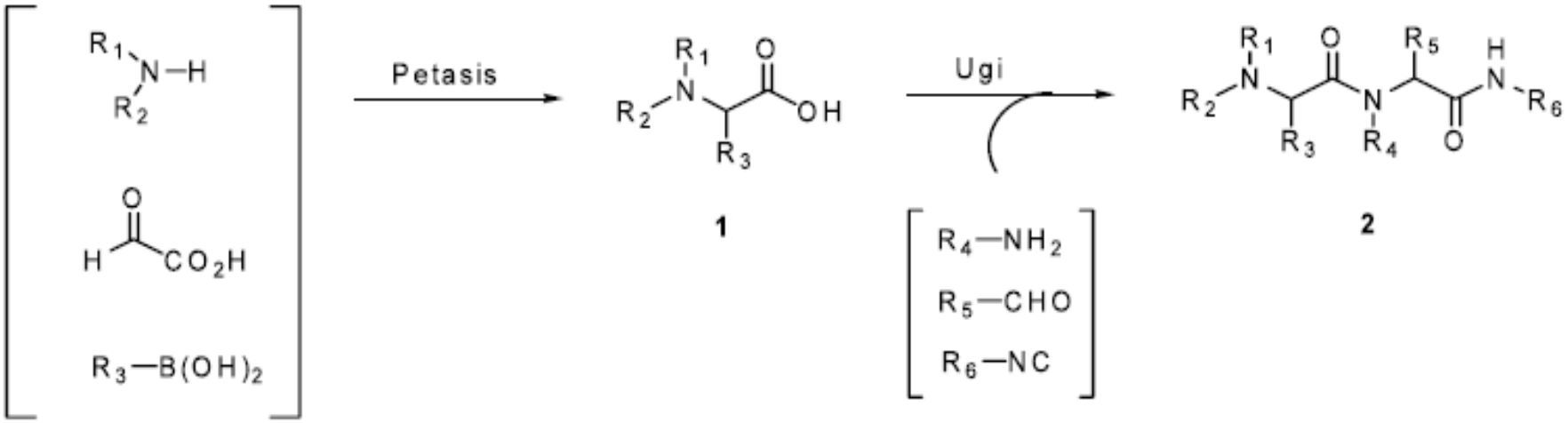
Multicomponent Reactions



- Multicomponent Reactions (MCRs) are general defined as reactions where more than two starting materials to react to form a product, incorporating essentially all of the atoms of the educts.
- Generally, there are different classification schemes of MCRs possible, e.g. according to the **reaction mechanisms**, the **components** involved, or the intrinsic **variability.**

Diversity in Multicomponent Reactions

- The union of two highly variable MCRs, the Petasis and Ugi reaction:



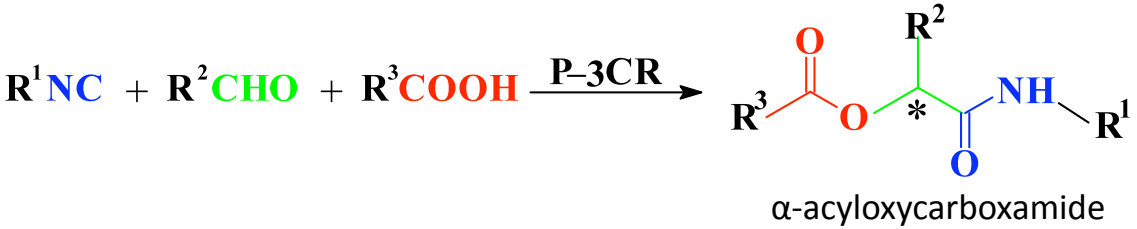
- Since both reactions use starting material which are commercially available in very large quantities. Theoretically, this combination of MCRs spans a chemical space of greater than $1000 \times 200 \times 500 \times 1000 \times 1000 = 10^{14}$ small molecules. This constitutes a combination of MCRs of very high variability.
- An interesting fact about isocyanides:

  The more long-term inhalation of isocyanides is said to increase the intensity of dreams at night.

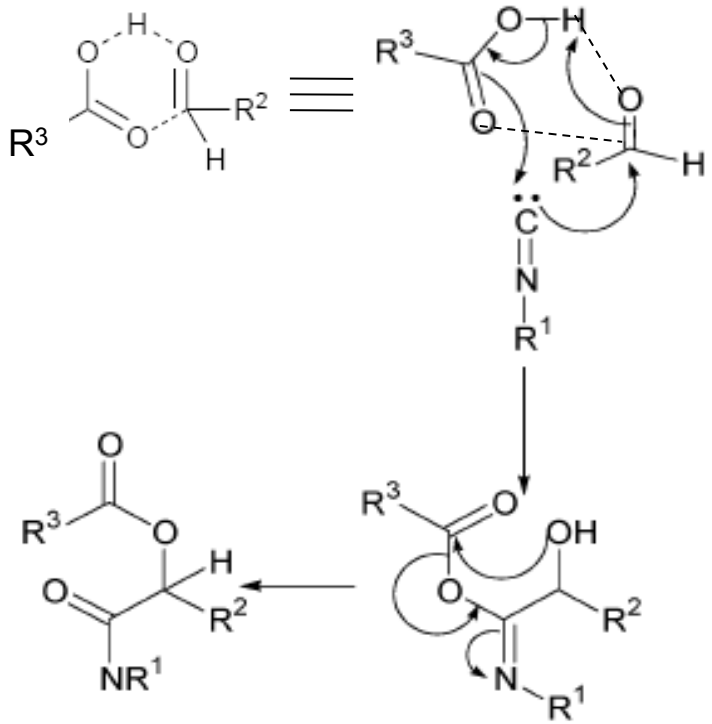
Portlock, D. E.; Naskar, D.; West, L.; Ostaszewski, R.; Chen, J. J.*Tetrahedron Lett.* **2003,** *44*, 5121.

The Passerini Reaction (developed in 1921)

- Mario Passerini (1881-1962), the inventor of one of the most significant isocyanide based MCRs.



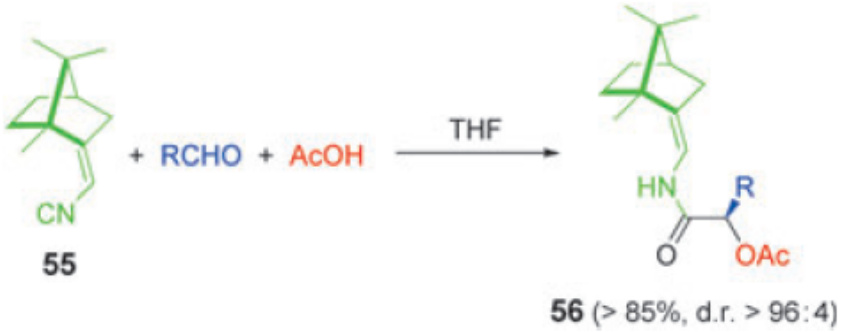
Mechanism of Passerini Reaction



- Accelerated in aprotic solvents needed: THF, DCM, MeCN etc.

Diastereoselective Passerini Reaction

Chiral Isocyanides

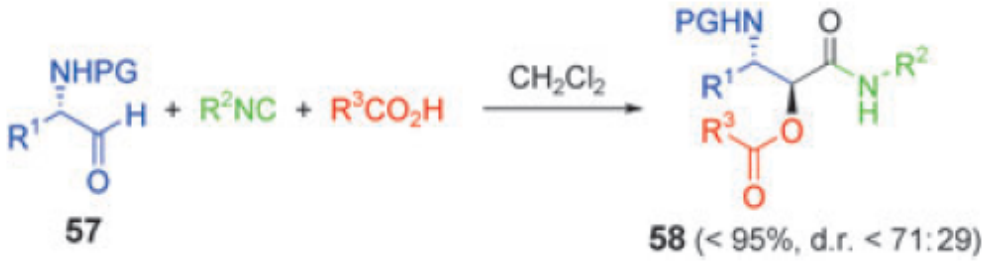


55

56 (> 85%, d.r. > 96:4)

H. Bock, I. Ugi, *J. Prakt. Chem*. **1997**, *339*, 385.

Chiral Aldehydes

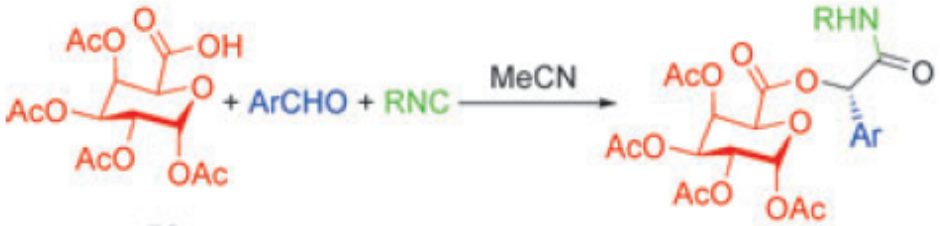


57

58 (< 95%, d.r. < 71:29)

L. Banfi, G. Guanti, R. Riva, *Chem. Comm*. **2000**, 985.

Chiral Acids



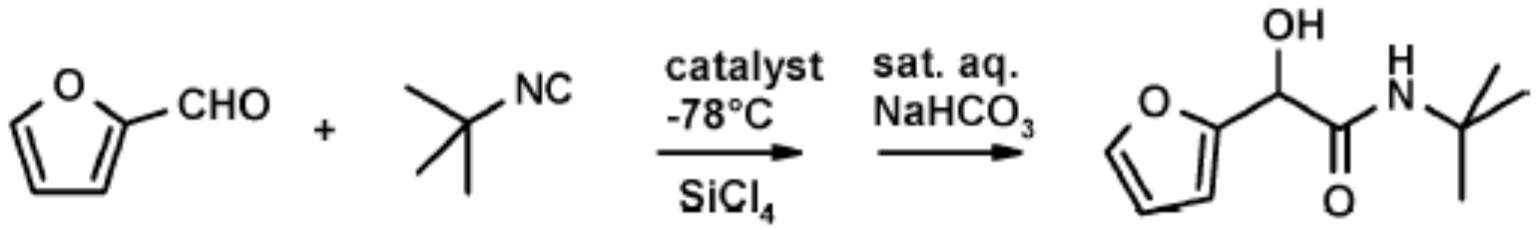
59

60 (d.r. < 98:2)

R. Frey, S. G. Galbraith, S. Guelfi, C. Lamberth, M. Zeller, *Synlett* **2003**, 1536.

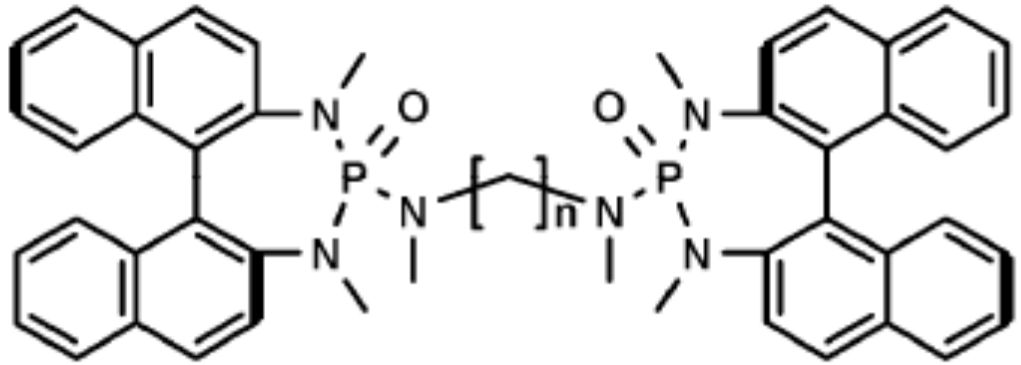
Enantioselective Passerini-Type Reaction

Denmark's Highly Enantioselective P-2CR of Mandelamides



49 23 50 er = 96:4 yield 76%

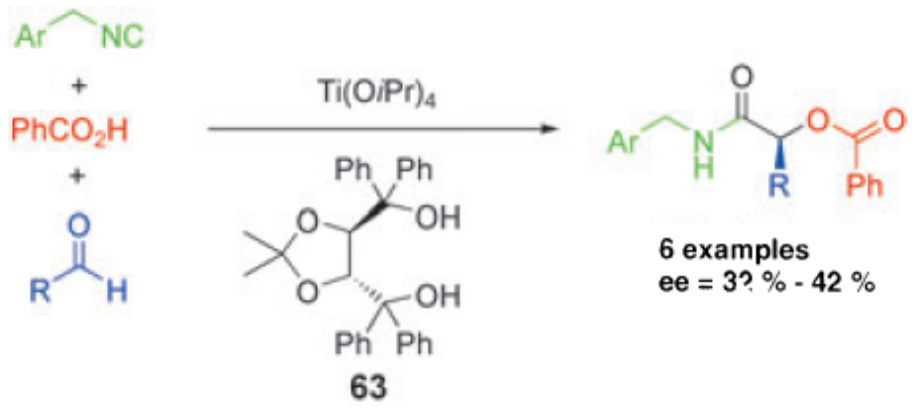
catalyst:



n = 4-6

Denmark, S.E.; Fan, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7825
Denmark, S.E.; Fan, Y. *J. Org. Chem.* **2005**, *70*, 9667

Enantioselective Passerini Reaction (1)



Catalyst loading: 100 mol% or 50 mol%

$Ti(O^iPr)_4$: Ligand = 1:1

U. Kusebauch, B. Beck, K. Messer, E. Herdtweck, A. Domling *Org. Lett*. **2003**, *5*, 4021.

Enantioselective Passerini Reaction (1)

Solvents

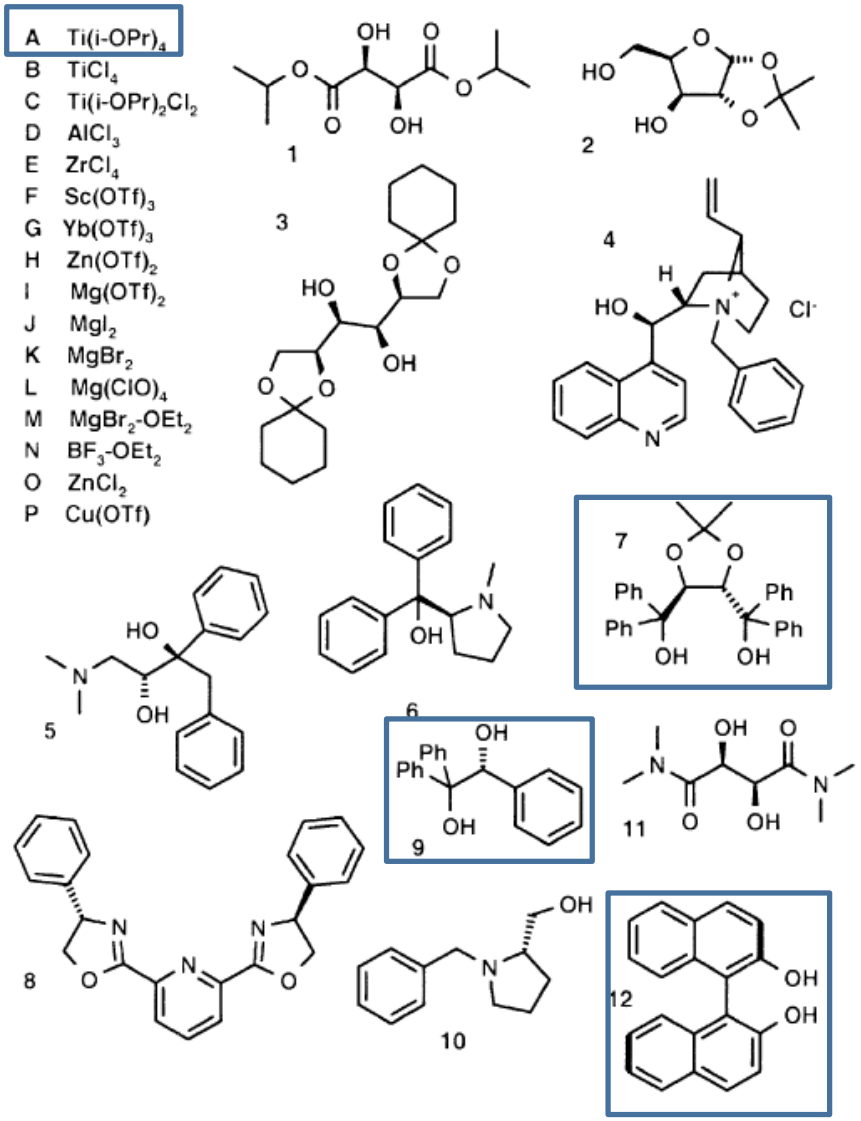
Ether

THF

DCM

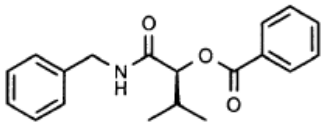
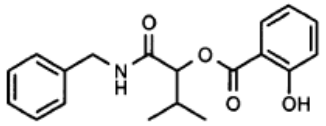
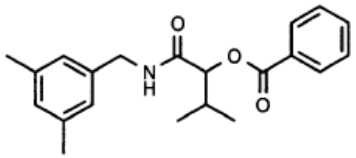
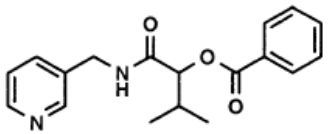
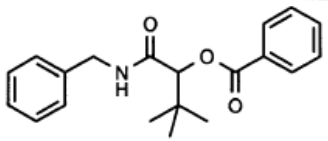
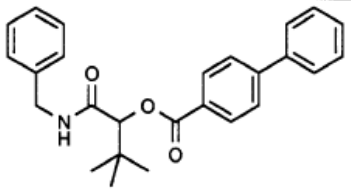
Toluene

Dioxane

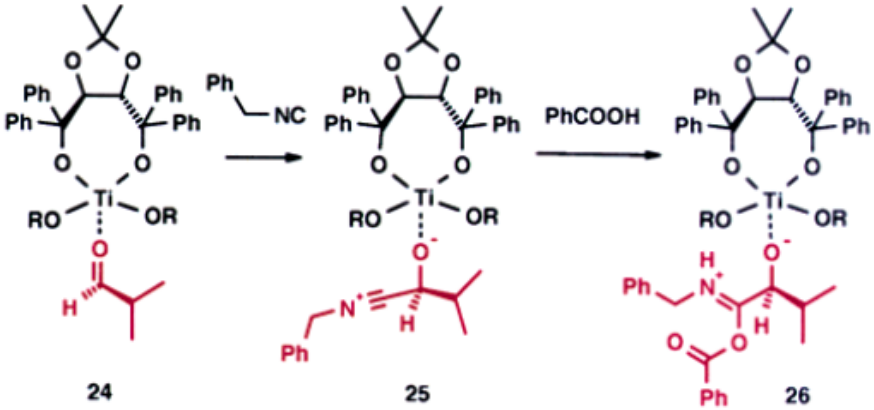


U. Kusebauch, B. Beck, K. Messer, E. Herdtweck, A. Domling *Org. Lett*. **2003**, *5*, 4021.

Enantioselective Passerini Reaction (1)

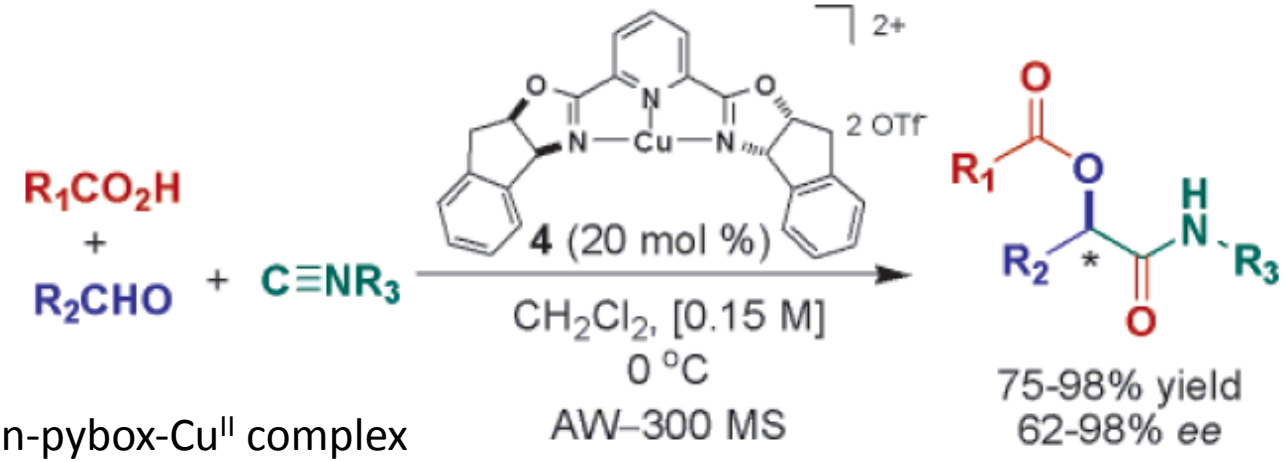
Comp. no.	Structure	Yields (%)	ee (%)
16		46[a] (86)[b]	36[c]
17		12 (93)	32
18		31 (47)	32
19		28 (76)	42
20		48 (81)	34
21		46 (95)	36

[a] Isolated yield of the Passerini reaction performed on a 1 mmol scale with **A7**. [b] In brackets: isolated yield of the Passerini reaction performed on a 5 mmol scale without **A7**. [c] Enantiomeric excess of the Passerini reaction performed with **A7**.

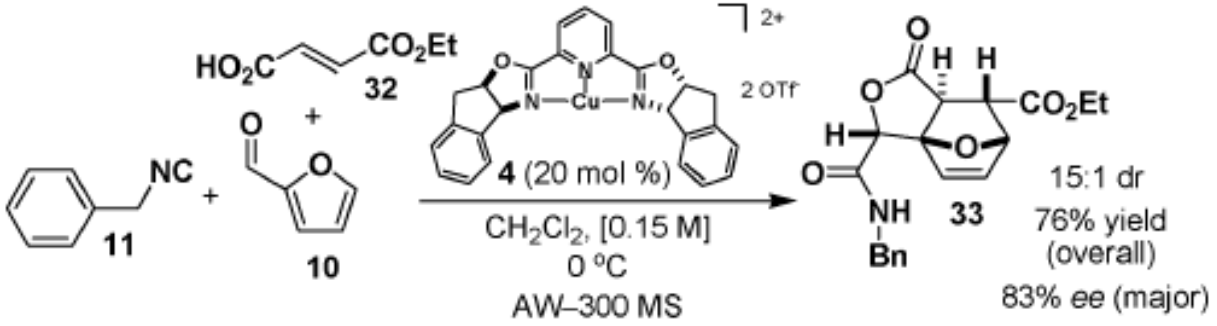


U. Kusebauch, B. Beck, K. Messer, E. Herdtweck, A. Domling *Org. Lett*. **2003**, *5*, 4021.

Enantioselective Passerini Reaction (2)

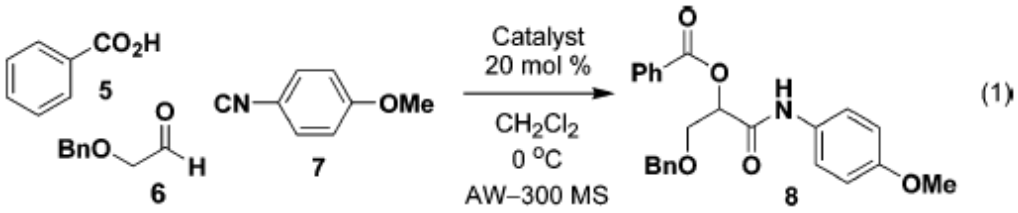


4 = indan-pybox-Cu^{II} complex



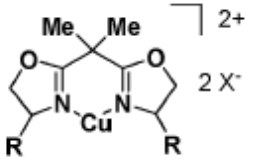
Andreana, P.R.; Liu, C.C.; Schreiber, S.L. *Org. Lett*. **2004**, *6*, 4231.

Enantioselective Passerini Reaction (2)



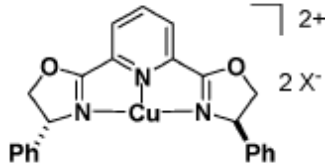
entry[a]	catalyst[b]	time (h) (0 °C)	[conc] (M)	% yield[c]	% ee[d]
1	**1a**	18	0.25	71	50
2	**1b**[e]	18	0.25	63	56
3	**2a**	14	0.50	93	64
4	**2b**[e]	8	0.50	87	63
5	**3a**	18	0.25	90	85
6	**3b**[e]	18	0.25	86	79
7	**4**[f]	**18**	**0.15**	**93**	**97**
8	*g*	36 (40 °C)	0.15	<5	ND
9	*h*	36 (40 °C)	0.15	<5	ND

[a] **6** was premixed with 20 mol % catalyst and cooled to 0 °C. [b] Homogeneous solution. [c] Isolated by column chromatography. [d] Determined by HPLC using a Chiralcel OD column. [e] AgCl was removed using a GHP Acrodisc 13 0.20 μm filter. [f] For optimal ee's, the ligand was crystallized prior to use. [g] $Cu(OTf)_2$ only. [h] Ligand of **4** only. ND, not determined.

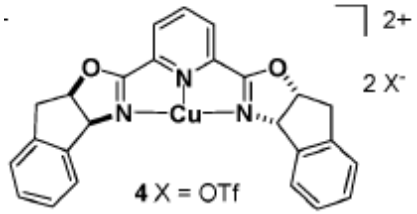


1a R = (*S*) ^{t}Bu, X = OTf
1b R = (*S*) ^{t}Bu, X = SbF_6
2a R = (*S*) Ph, X = OTf
2b R = (*S*) Ph, X = SbF_6

bidentate (*S,S)*-bis(oxazolinyl) (box) (**1** & **2**)-Cu(II)



3a X = OTf
3b X = SbF_6



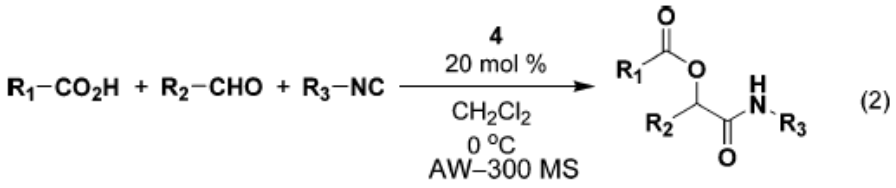
4 X = OTf

tridentate bis(oxazolinyl)pyridine (pybox) (**3** & **4**)-Cu(II)

- Anhydrous conditions were necessary to avoid background reaction by water)

Andreana, P.R.; Liu, C.C.; Schreiber, S.L. *Org. Lett*. **2004**, *6*, 4231.

Enantioselective Passerini Reaction (2)



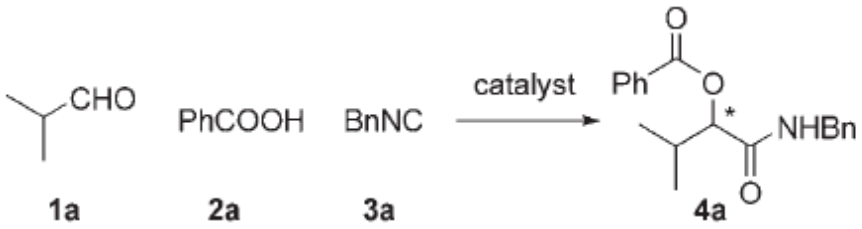
entry[a]	R_1	R_2	R_3	product	% yield[b]	% ee[c]
1	$PhCH_2$ (**9**)	2-furyl (**10**)	$PhCH_2$ (**11**)	**16**	83	62 (*R*)[d]
2	$PhCH_2$ (**9**)	$BnOCH_2$ (**6**)	$PhCH_2$ (**11**)	**17**	87	72
3	Ph (**5**)	2-thiophenecarboxyl (**12**)	*t*-butyl (**13**)	**18**	95	82 (*R*)
4	Ph (**5**)	$BnOCH_2$ (**6**)	*n*-butyl (**14**)	**19**	87	88
5	Ph (**5**)	$BnOCH_2$ (**6**)	*n*-pentyl (**15**)	**20**	83	89
6	Ph (**5**)	$BnOCH_2$ (**6**)	$PhCH_2$ (**11**)	**21**	89	93
7	Ph (**5**)	$BnOCH_2$ (**6**)	*t*-butyl (**13**)	**22**	95	98
8	Ph (**5**)	2-furyl (**10**)	*p*-MeOPh (**7**)	**23**	98	91 (*R*)
9	Ph (**5**)	2-furyl (**10**)	$PhCH_2$ (**11**)	**24**	90	75 (*R*)
10	Ph (**5**)	2-furyl (**10**)	*t*-butyl (**13**)	**25**	97	89 (*R*)
11	Ph (**5**)	2-furyl (**10**)	*n*-butyl (**14**)	**26**	82	78 (*R*)
12	Ph (**5**)	2-furyl (**10**)	*n*-pentyl (**15**)	**27**	82	78 (*R*)
13	Ph (**5**)	2-thiophenecarboxyl (**12**)	*p*-MeOPh (**7**)	**28**	95	89 (*R*)
14	Ph (**5**)	2-thiophenecarboxyl (**12**)	$PhCH_2$ (**11**)	**29**	87	75 (*R*)
15	Ph (**5**)	2-thiophenecarboxyl (**12**)	*n*-butyl (**14**)	**30**	76	64 (*R*)
16	Ph (**5**)	2-thiophenecarboxyl (**12**)	*n*-pentyl (**15**)	**31**	75	60 (*R*)

[a] [0.15 M] final. [b] Isolated yield. [c] See the Supporting Information for HPLC conditions. [d] Inferred absolute stereochemistry based on X-ray crystal analysis with 5-bromo-2-furaldehyde as the substrate.

- Limitation: Chelating aldehydes needed, no diversity in acid component

Andreana, P.R.; Liu, C.C.; Schreiber, S.L. *Org. Lett*. **2004**, *6*, 4231.

Enantioselective Passerini Reaction (3)

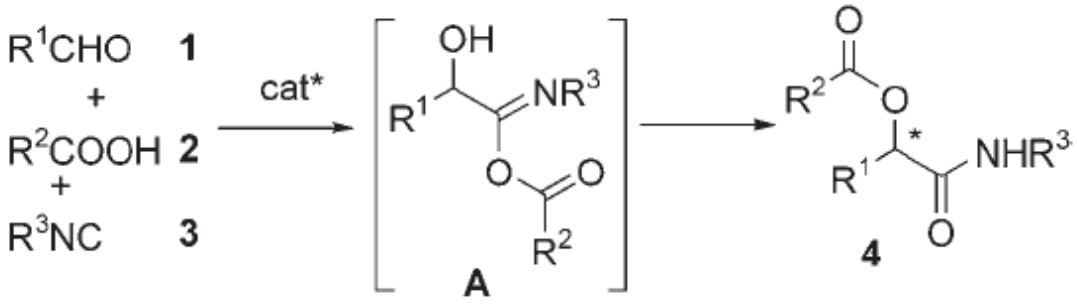


16 examples

Ligand/Catalyst	Conditions	Yield (%)	ee(%)
 **5a**	10 mol % Et_2AlCl + ligand toluene, - 40 °C, 48 h	51-70	63-99

Wang, S.-X.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Angew. Chem. Int. Ed*. **2008**, *47*, 388

Enantioselective Passerini Reaction (3)



Possible Solution:
To use a chiral catalyst with a single coordination site
&
Slow addition of the acid component to avoid the background reaction

<u>Several pitfalls exist that make this task particularly challenging:</u>

1) The complexity of the reaction mechanism

2) The competitiveness of the uncatalyzed background reaction

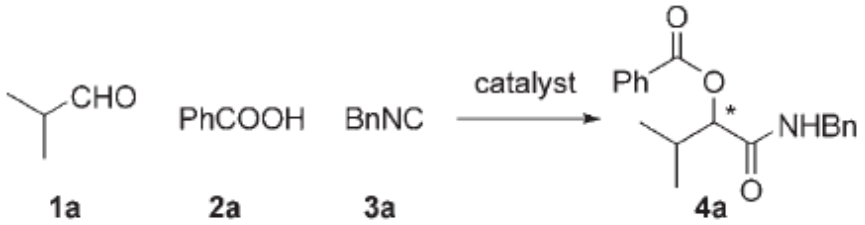
3) The potential of the three components, all of which are Lewis bases, to coordinate to or deactivate the catalyst

4) The problem of catalyst turnover as a result of product inhibition. The P-3CR adduct itself is also a bidentate ligand and can therefore compete with the substrate to coordinate to the catalyst

5) When a nonchelating aldehyde is used, the reaction produces an imidate intermediate **A** that is bidentate in nature.

Wang, S.-X.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Angew. Chem. Int. Ed*. **2008**, *47*, 388

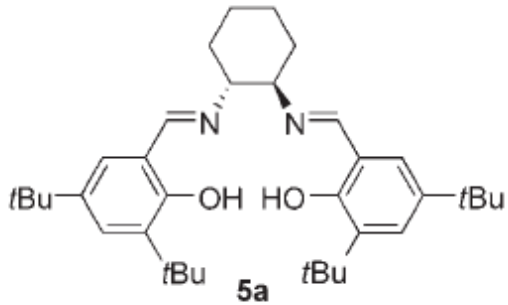
Enantioselective Passerini Reaction (3)



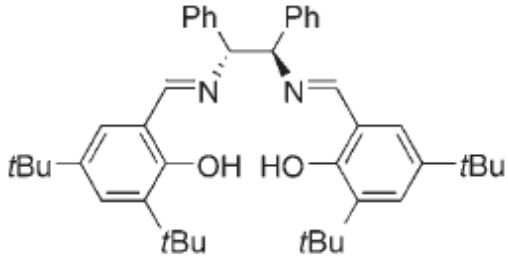
Entry	Catalyst	T [°C]	Yield [%][b]	*ee* [%][c]
1	none	−40	37	rac.
2	**5a** + Et_2AlCl	−40	70	63
3	**5a** + Et_3Al	−40	32	8
4	**5a** + $MnCl_3$	−40	36	19
5	**5a** + $CrCl_3$	−40	54	24
6	**5a** + $Ti(OiPr)_4$	−40	trace	n.d.[d]
7	**5a** + Et_2Zn	−40	35	0
8	**5a** + Et_2AlCl	−20	51	53
9	**5a** + Et_2AlCl	−60	26	80
10[e]	**5a** + Et_2AlCl	−40	50	59
11[f]	**5a** + Et_2AlCl	−20	71	47
12	**5b** + Et_2AlCl	−40	66	51

[a] General conditions: **1a**/**2a**/**3a** 1:1:1, 48 h, c = 0.33 M, toluene. [b] Yield of the analytically pure product. [c] Determined by HPLC analysis on a chiral phase. [d] Not determined. [e] The reaction was performed at a concentration of 0.1 M. [f] The reaction was performed in CH_2Cl_2. Bn = benzyl.

<u>Optimized Conditions</u>
Concentration = 0.33M
Solvent = toluene
Tempearture = - 40 °C
Time = 48 h
Slow addition of acid



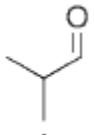
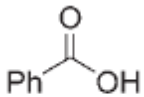
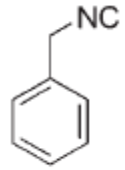
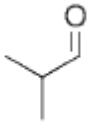
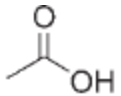
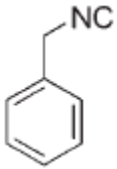
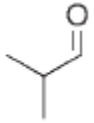
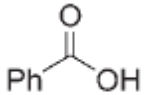
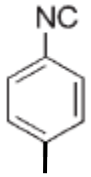
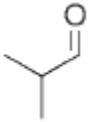
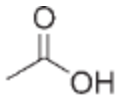
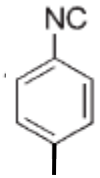
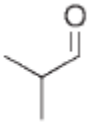
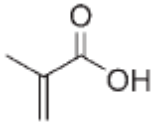
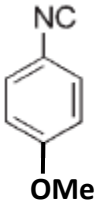
5a



5b

Wang, S.-X.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Angew. Chem. Int. Ed*. **2008**, *47*, 388

Enantioselective Passerini Reaction (3)

Entry	Aldehyde	Acid	Isocyanide	Yield [%]	*ee* [%]
1				70 (53%)*	63
2				59	63
3				63	84
4				60	84
5				62	80

* ^{t}BuNC used

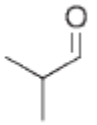
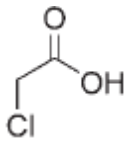
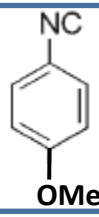
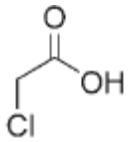
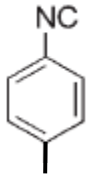
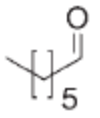
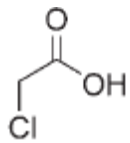
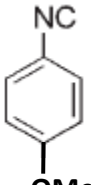
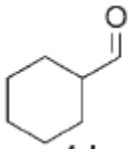
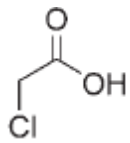
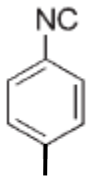
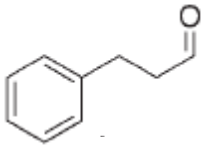
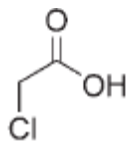
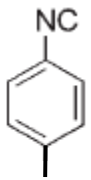
Variations

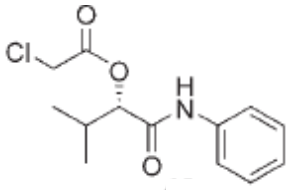
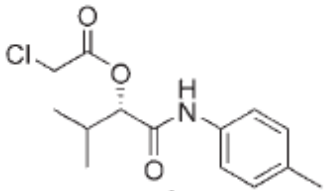
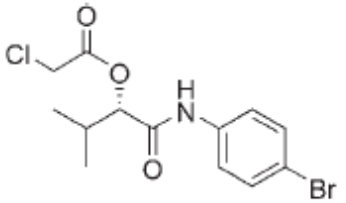
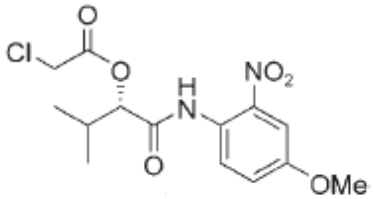
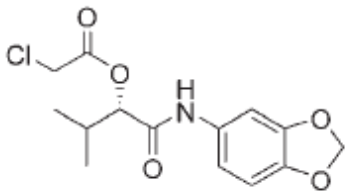
Acid and Isocyanide

(Aromatic aldehydes Failed)

Wang, S.-X.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Angew. Chem. Int. Ed*. **2008**, *47*, 388

Enantioselective Passerini Reaction (3)

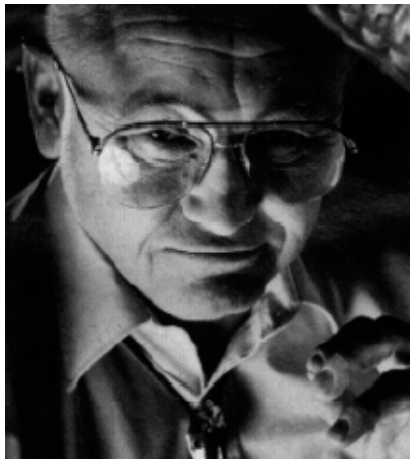
Entry	Aldehyde	Acid	Isocyanide	Yield [%]	*ee* [%]
7				64	> 99
8				66	87
9[b]				67	73
10				59	87
11[b]				68	71

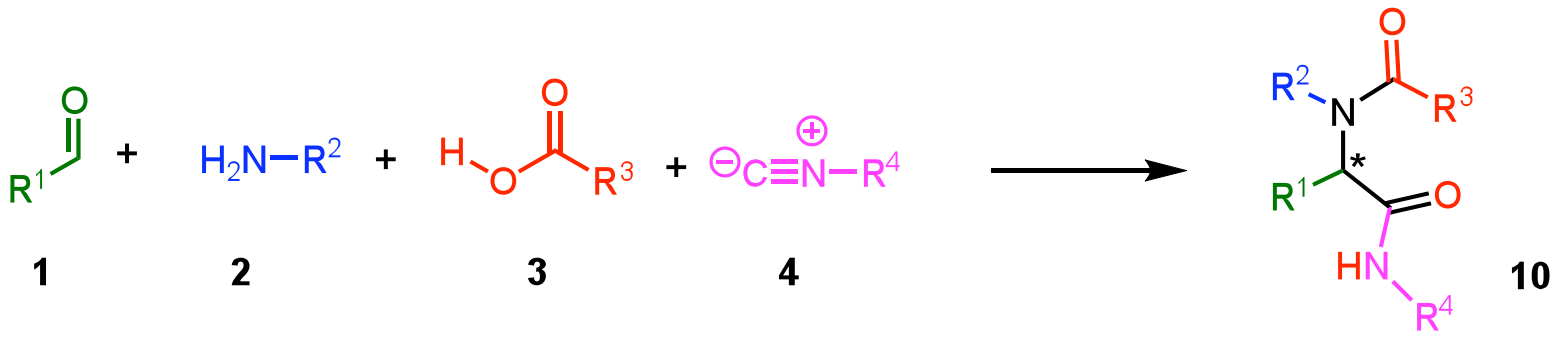
		Yield [%]	*ee* [%]
12[b]		68	93
13		61	81
14[b]		52	88
15[c]		66	75
16		64	68

Wang, S.-X.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Angew. Chem. Int. Ed*. **2008**, *47*, 388

The Ugi Reaction

- Ivar Karl Ugi (1930-2005), the inventor of the most diversified IMCRs.

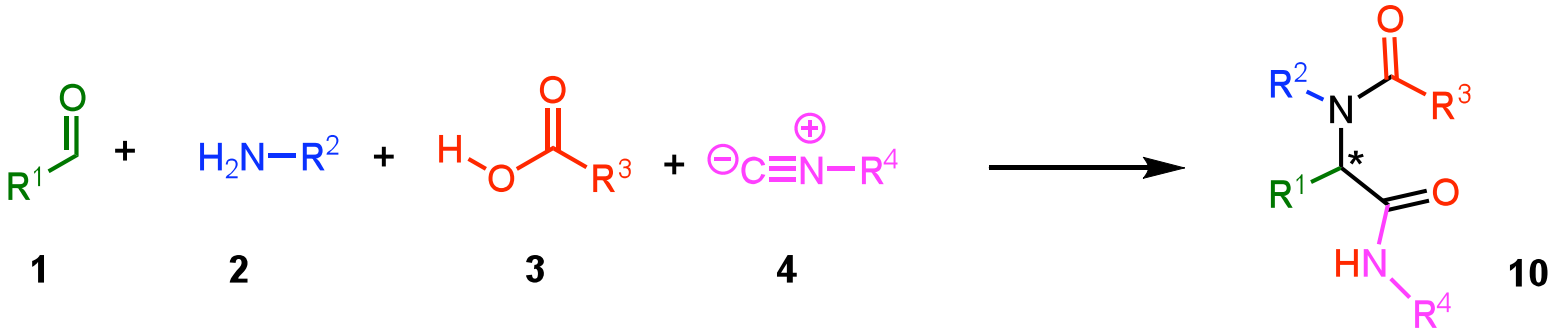


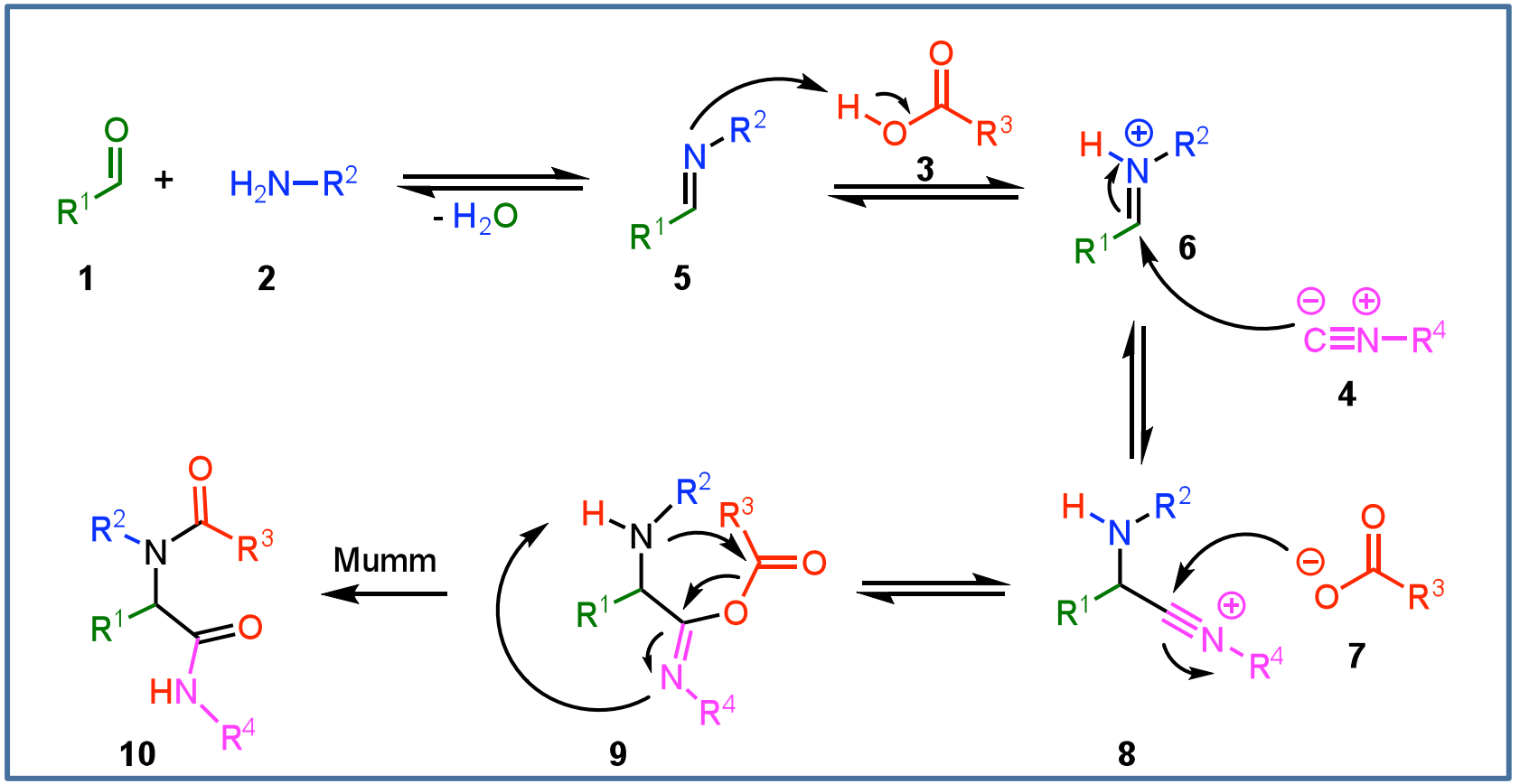


α-*N*-acylamino amide

Ugi, I. *Angew. Chem. Int. Ed.* **1962**, *1*, 8.

The Ugi Reaction





Four Component Approach
Ugi Reaction

General Requirements for Ugi Reaction

- Highly nucleophilc amine recommended
- Electron rich aldehydes favor the reaction. Preformed Imines from ketones also react (Yamada, 1998, synthesis, 991)
- Strong Acids
- Usually at room temperatures. Low temp sometimes(Ugi, 1991,Synthesis, 1095)
- High Concentration of the reactants
- Pre-formation of imines gives good yields.
- Polar solvents like Methanol. Toluene (with high temp), ether and CH_2Cl_2 are also used.
- High Pressure

Ugi Reaction in Toluene

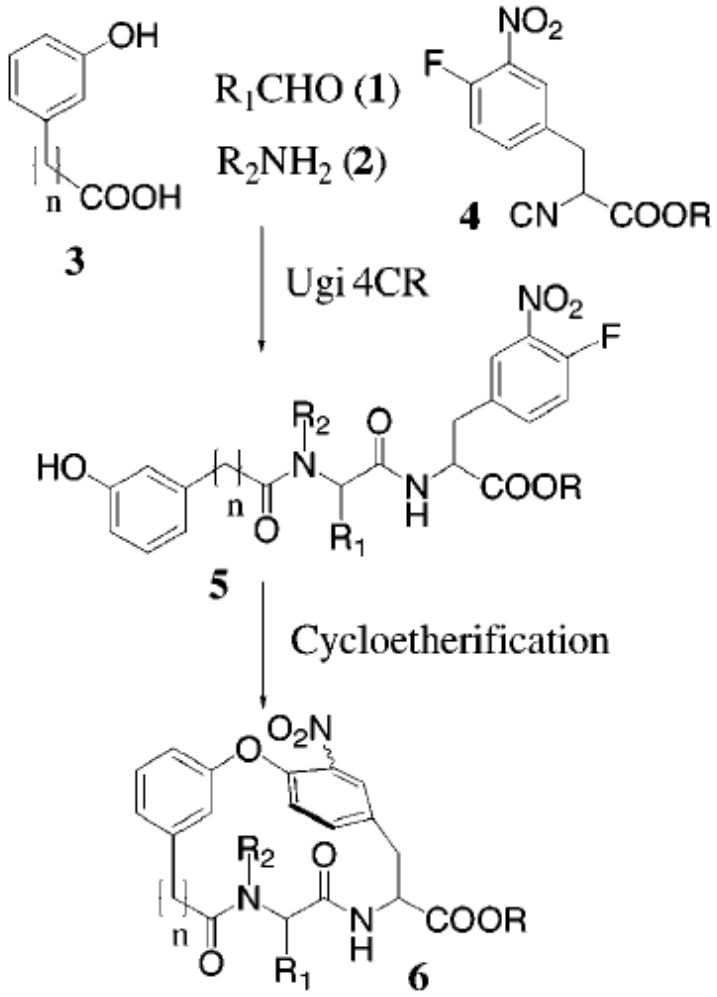


Table 1. Survey of Conditions for Ugi 4CR[a]

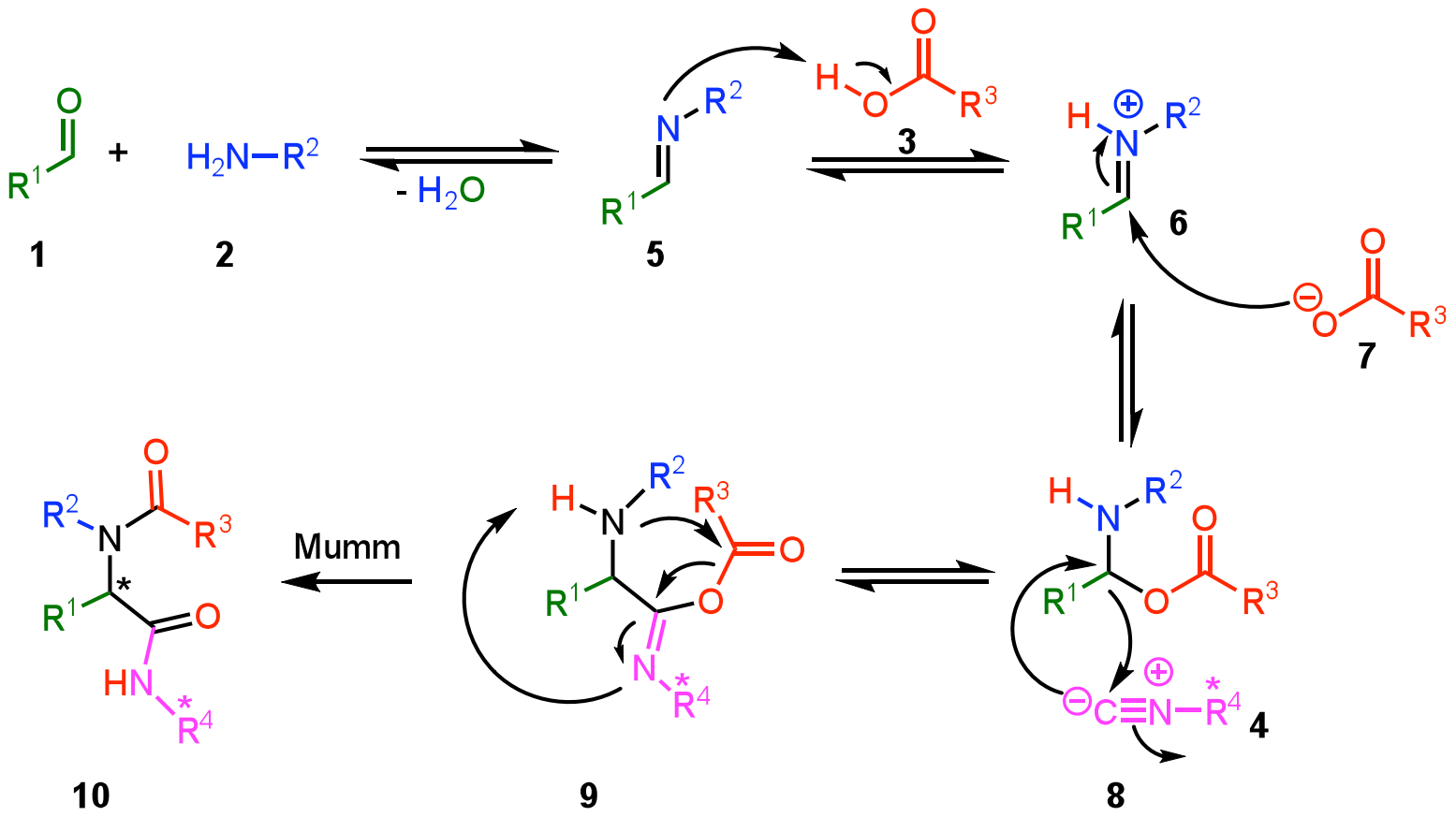
entries	solvent	*T*, °C	additive	yield, %[b]
1	MeOH	rt[c]	none	34[d]
2	MeOH	60	none	16[e]
3	DMF[f]	rt	none	0
4	CF_3CH_2OH	rt	none	71
5	benzene	reflux[g]	none	76
6	toluene	60	none	50
7	toluene	60	NH_4Cl	60
8	toluene	rt	NH_4Cl	33[h]
9	toluene	60	LiBr	35
10	THF[f]	60	NH_4Cl	39

[a] 2.2 equiv each of amine, aldehyde, and acid relative to isonitrile was used. [b] Total yield of two diastereomers in a 1/1 ratio. [c] Room temperature. [d] 83% conversion of **4a** after 24 h. [e] Isonitrile was consumed rapidly, leading to a complex reaction mixture. [f] DMF = *N*,*N*-dimethylformamide, THF = tetrahydrofurane. [g] With Dean−Stark. [h] 63% conversion of **4a** after 48 h.

Cristau, P., Vors, J.P. & Zhu, J. *Org. Lett*. **2001,** *3*, 4079.

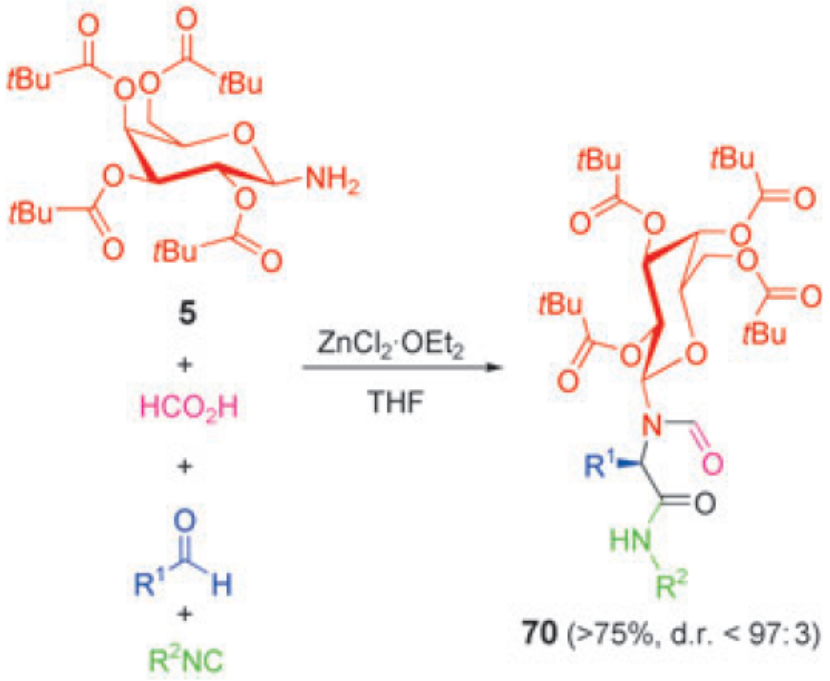
Diastereoselective Ugi Reaction: Chiral Isocyanides

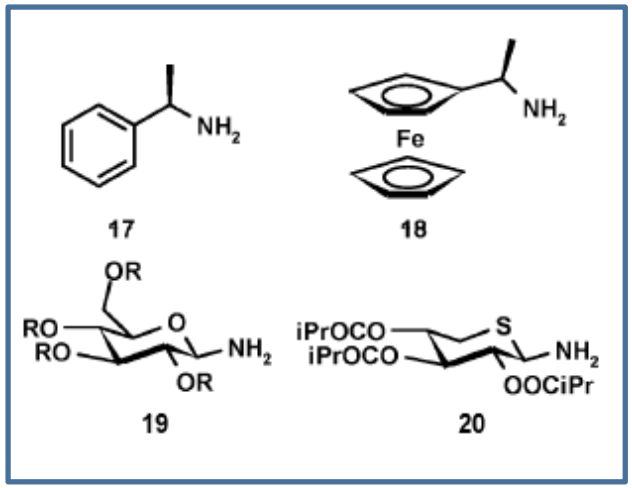
Alternate Mechanism:

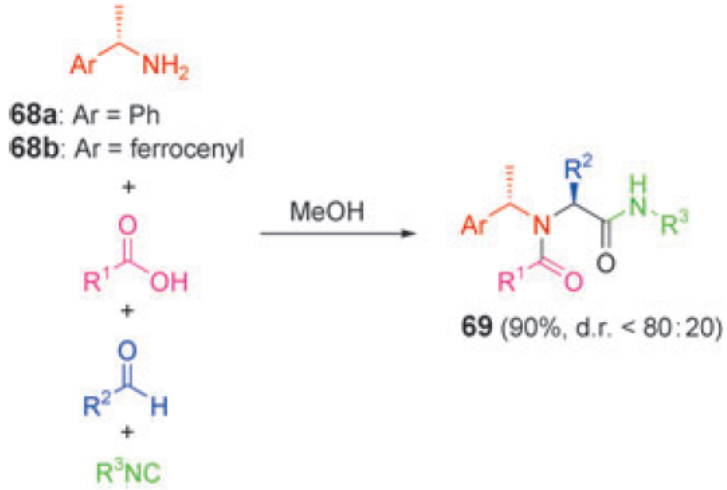


Banfi, L., Basso, A., Guanti, G. & Riva, R. Asymmetric isocyanide-based MCRs. In Multicomponent Reactions (eds. Zhu, J. & Bienayme´, H.) 1–32 (Wiley-VCH, Weinheim, Germany, **2005**).

Diastereoselective Ugi Reaction: Chiral Amines





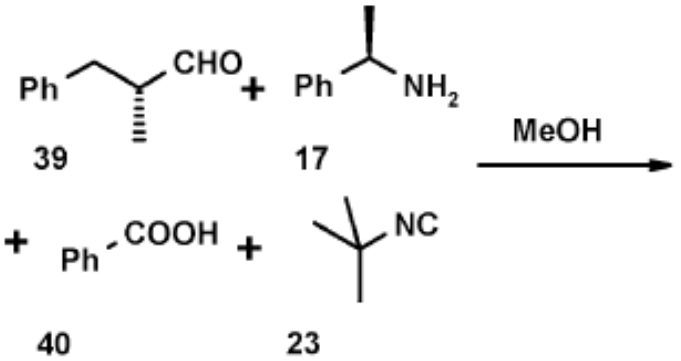


Ugi, K. Offermann *Angew. Chem. Int. Ed. Engl*. **1963**, *2*, 624.

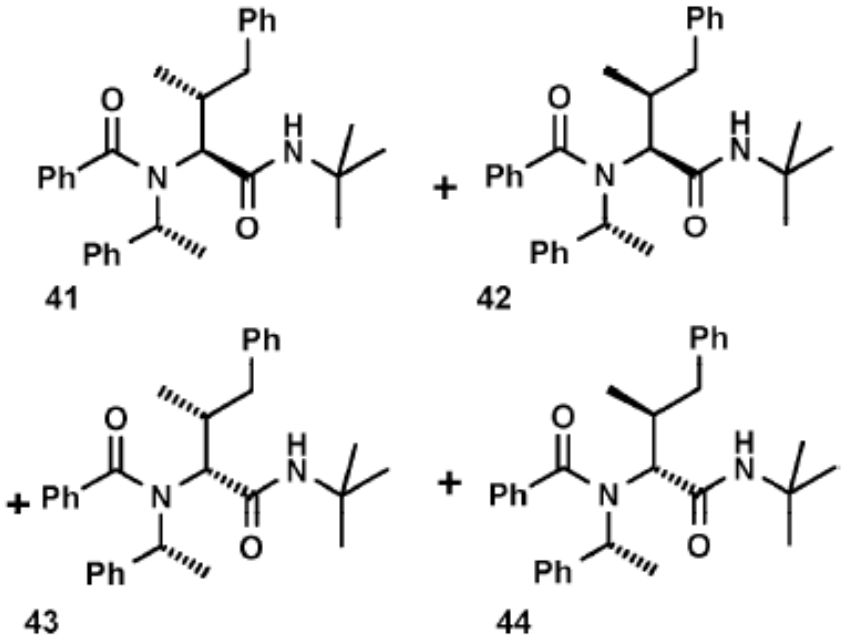
D. Marquarding, P. Hoffmann, H. Heitzer, I. Ugi, J. Am. Chem. Soc. **1970**, *92*, 1969.

Diastereoselective Ugi Reaction: Chiral Aldehydes

Potential Racemization of Certain Aldehydes with a Stereocenter in the α-Position during the U-4CR



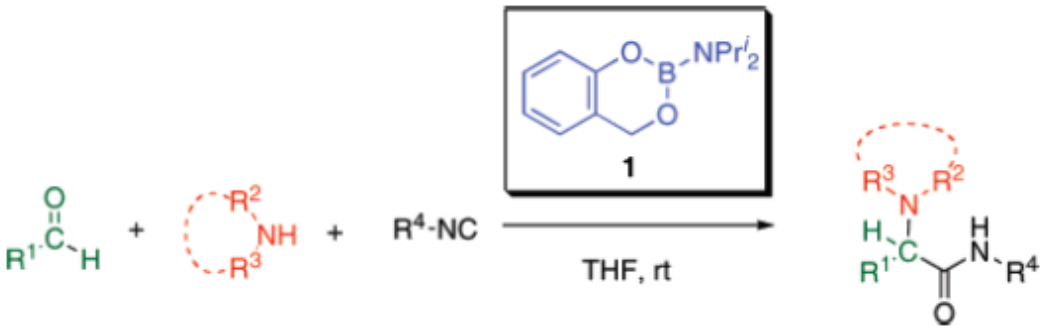
No racemization if OBn or OTBDMS at C-2 position of aldehyde



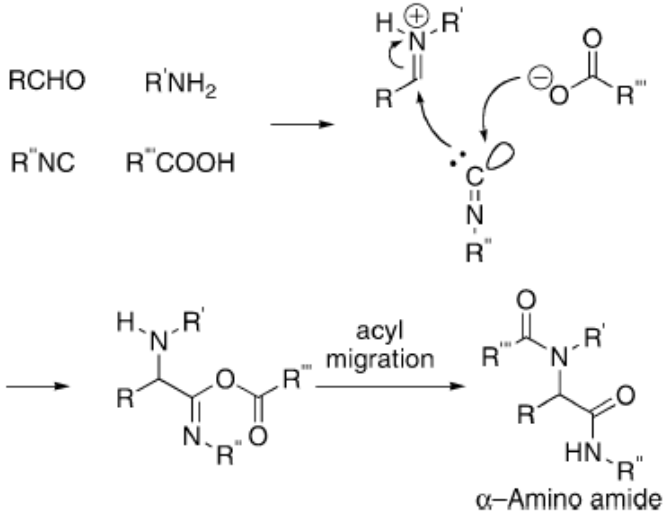
Kelly, C. L.; Lawrie, K. W. M.; Morgan, P.; Willis, C. L. *Tetrahedron Lett.* **2000**, *41*, 8001.

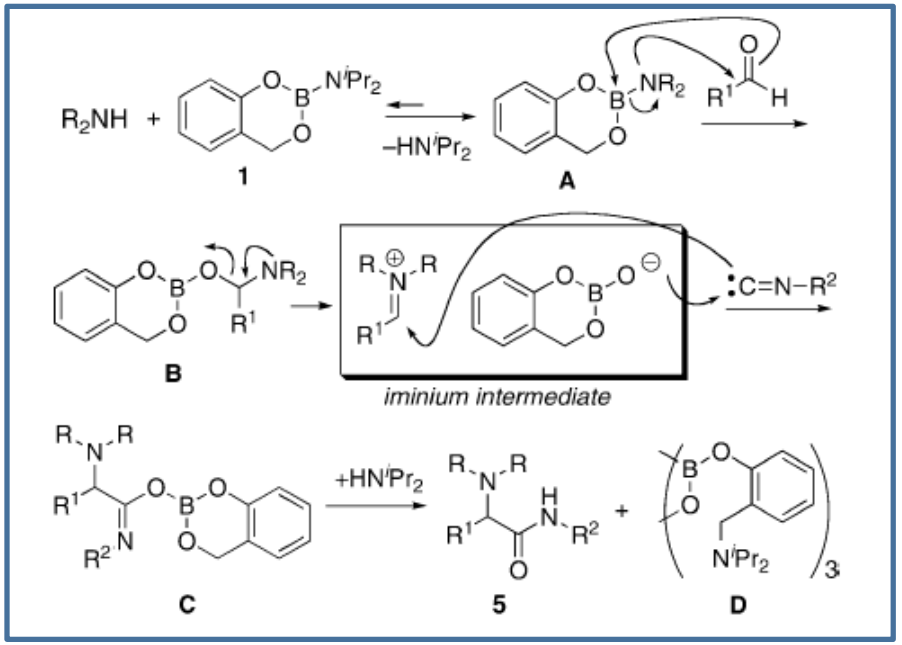
Three Component Approach
Ugi Reaction

Acid-Free Three Component Ugi Reaction Utilizing Secondary Amines



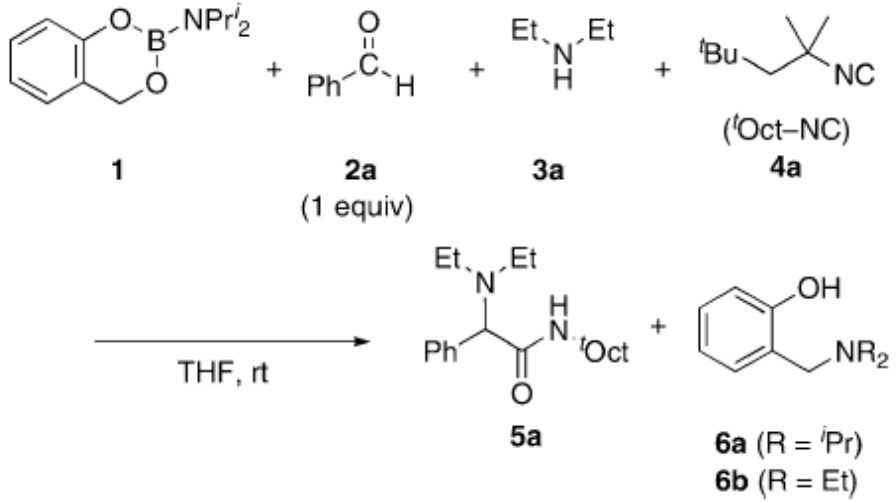
Scheme 1. Acid-Mediated Ugi Four-Component Coupling Reaction





Tanaka, Y.; Hasui, T.; Suginome, M. *Org. Lett.* **2007**, *9*, 4407

Acid-Free Three Component Ugi Reaction Utilizing Secondary Amines

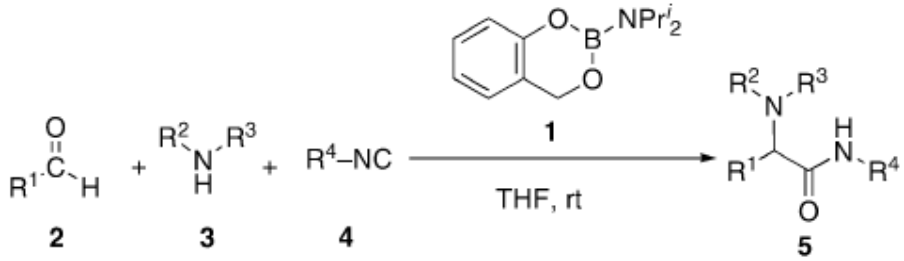


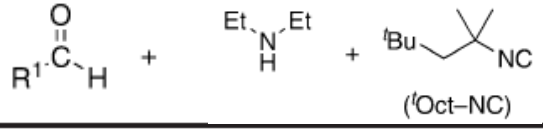
entry	equiv of **1**	equiv of **3a**	equiv of **4a**	% yield of **5a**[b,c]	% yield of **6**[b]
1	1	1	1.5	86	88 (**6a/6b** = 4:1)
2	1	1.5	1.5	94	89 (**6a/6b** = 3:1)
3	1	2	1.5	89	59 (**6b**)
4	1	1.5	2	77	67 (**6a/6b** = 1:4)
5	1.2	1.2	1.5	94	90 (**6a/6b** = 4:1)
6	1.5	1.5	1.5	99 (82)	89 (**6a/6b** = 4:1)
7[d]	0	2	1.5	0	0

[a] Benzaldehyde (0.2 mmol), Et_2NH, and *t*-octyl isocyanide were reacted with aminoborane **1** in THF at rt, unless otherwise noted. [b] NMR yield. [c] Isolated yield in the parentheses. [d] At 80 °C.

Tanaka, Y.; Hasui, T.; Suginome, M. *Org. Lett.* **2007**, *9*, 4407

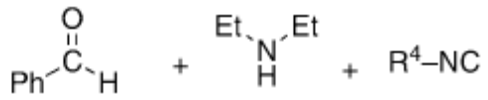
Acid-Free Three Component Ugi Reaction Utilizing Secondary Amines

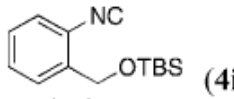
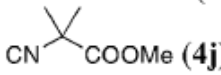




entry	R^{1}CHO	% yield[b]
1	4-BrC$_6$H$_4$CHO (**2b**)	81 (**5b**)
2	4-NO$_2$C$_6$H$_4$CHO (**2c**)	94 (**5c**)
3	4-MeOC$_6$H$_4$CHO (**2d**)	87 (**5d**)
4	4-BocNHC$_6$H$_4$CHO (**2e**)	83 (**5e**)
5	1-NapCHO (**2f**)	92 (**5f**)
6	2-PyrCHO (**2g**)	61 (**5g**)
7[c]	PhCH$_2$CH$_2$CHO (**2h**)	61 (**5h**)

[a] Aldehydes (0.4 mmol), diethylamine (0.6 mmol), and *tert*-octyl isocyanide (0.6 mmol) were reacted with aminoborane **1** (0.6 mmol) in THF (1 mL) at rt for 12−16 h, unless otherwise noted. [b] Isolated yield (silica gel column chromatography). [c] At 60 °C.



entry	R^4–NC	% yield [b]
1	4–MeOC$_6$H$_4$CH$_2$NC (**4b**)	95 (**5u**)
2	1–Adamantyl–NC (**4c**)	87 (**5v**)
3	4–EtOCOC$_6$H$_4$NC (**4d**)	94 (**5w**)
4	4–NO$_2$–2–Me–C$_6$H$_3$CHO(**4e**)	95 (**5x**)
5	4–MeOC$_6$H$_4$NC (**4f**)	96 (**5y**) [c]
6	4–TBSOOC$_6$H$_4$NC (**4g**)	90 (**5z**) [c]
7	MesNC (**4h**)	79 (**5aa**)
8	 (**4i**)	88 (**5ab**)
9	 (**4j**)	87(**5ac**)

[a] Benzaldehyde (0.4 mmol), diethylamine (0.6 mmol), and isocyanides (0.6 mmol) were reacted with aminoborane **1** (0.6 mmol) in THF (1 mL) at rt for 12−16 h, unless otherwise noted. [b] Isolated yield (silica gel column chromatography). [c] 0.8 mmol of diethylamine was used.

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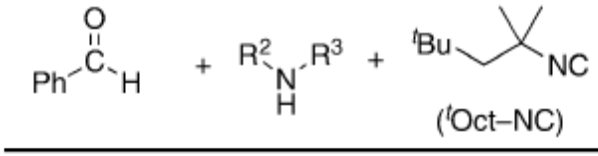
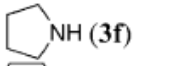
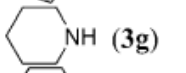
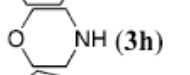
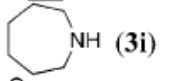
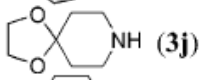
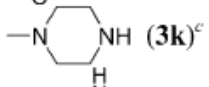
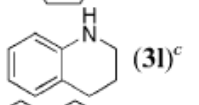
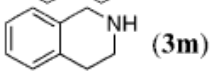
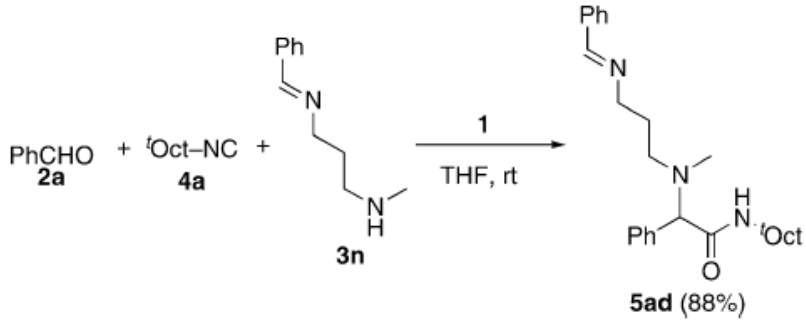
Acid-Free Three Component Ugi Reaction Utilizing Secondary Amines



entry	R^2R^3NH	% yield [b]
1	Bn_2NH (**3b**)[c]	85 (**5i**)
2	$(allyl)_2NH$ (**3c**)	81 (**5j**)
3	Ph(Me)NH (**3d**)[c]	86 (**5k**)
4	$^{i}Pr_2NH$ (**3e**)	58 (**5l**)
5	 (**3f**)	85 (**5m**)
6	 (**3g**)	94 (**5n**)
7	 (**3h**)	83 (**5o**)
8	 (**3i**)	83 (**5p**)
9	 (**3j**)	96 (**5q**)
10	 (**3k**)[c]	53 (**5r**)
11	 (**3l**)[c]	65 (**5s**)
12	 (**3m**)	87 (**5t**)

[a] **2** (0.4 mmol), **3** (0.6 mmol), and **4** (0.6 mmol) were reacted with aminoborane **1** (0.6 mmol) in THF (1 mL) at rt for 12−16 h, unless otherwise noted. [b] Isolated yield (silica gel column chromatography or preparative GPC (for **5r**)). [c] 0.8 mmol of the amine was used.

Major Difference from normal Ugi Reaction:
Non-acidic nature of the reaction system



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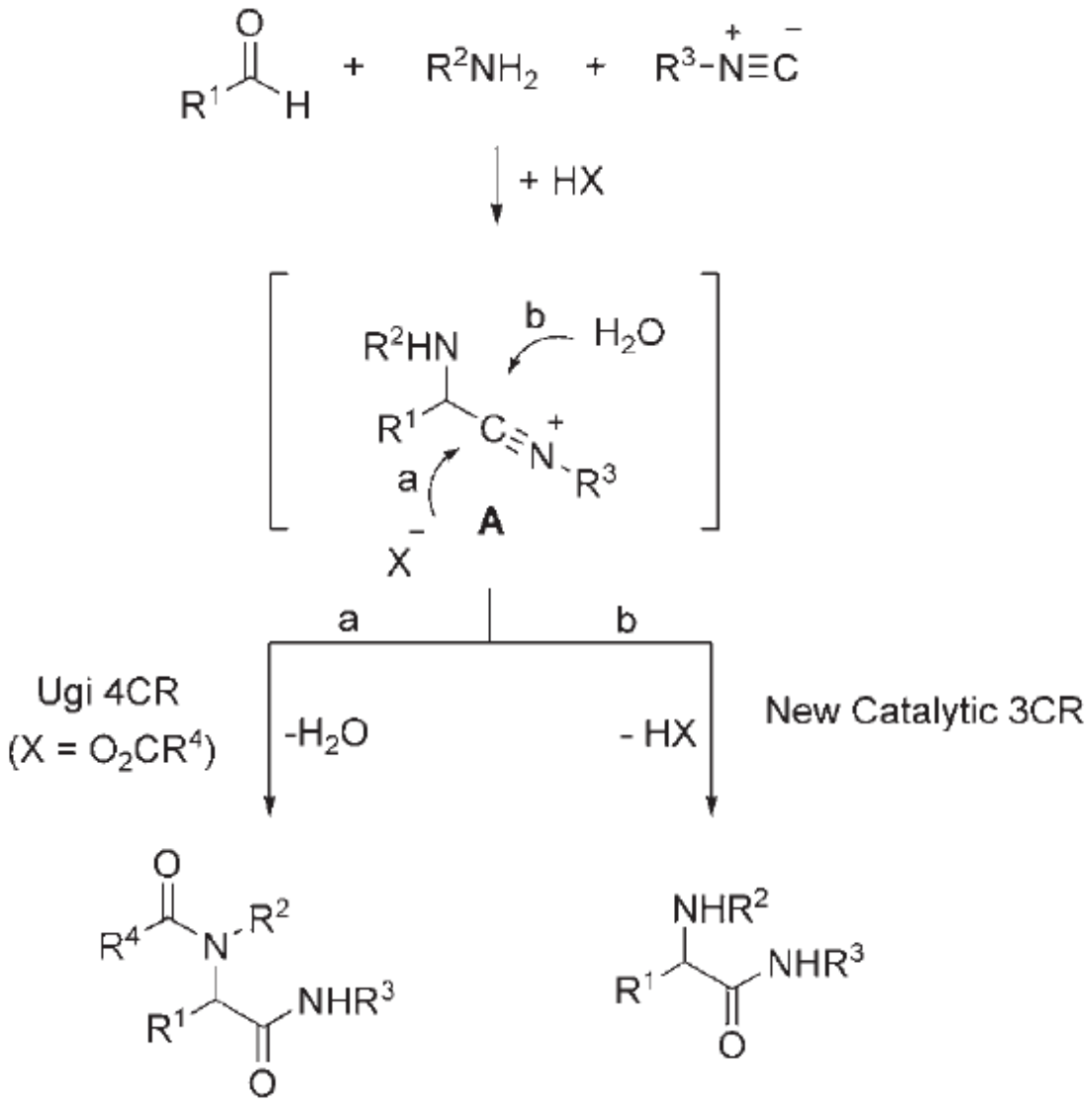
Catalytic Three-Component Ugi Reaction



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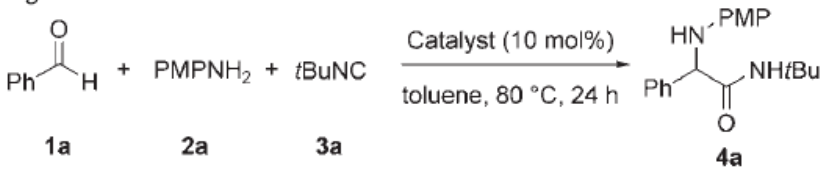
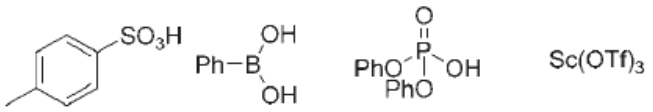
Catalytic Three-Component Ugi Reaction

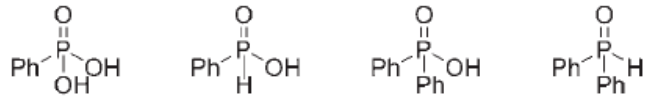
Table 1: Identification of an efficient catalyst for the three-component Ugi reaction.



1a 2a 3a 4a



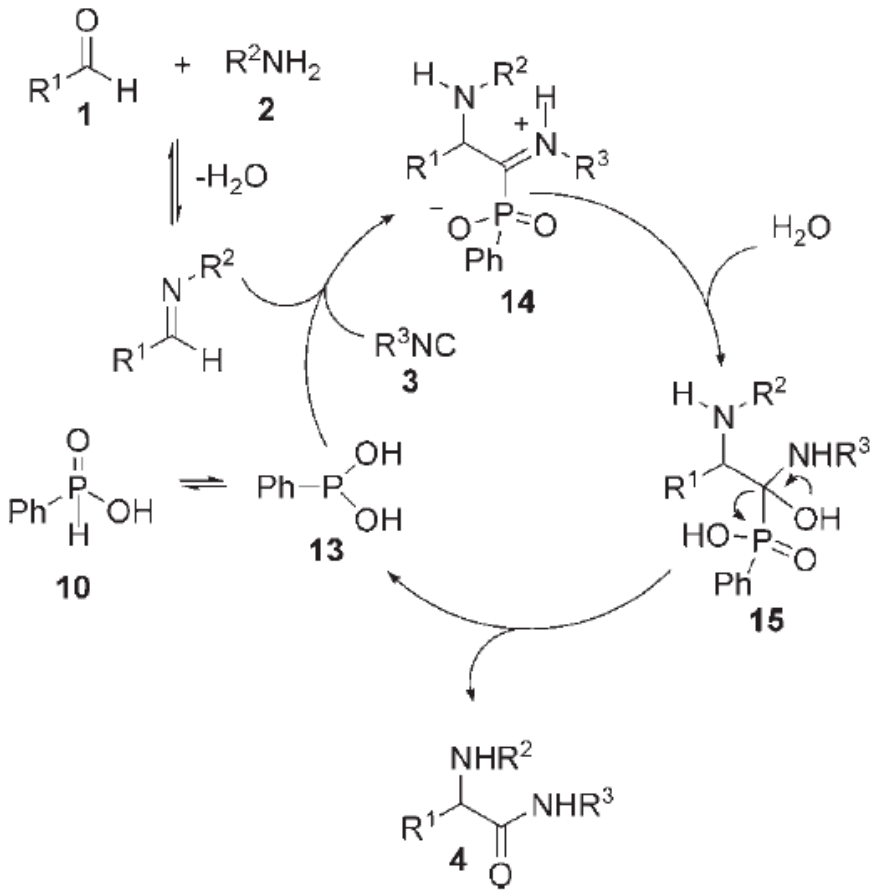
5 6 7 8



9 10 11 12

Entry	Catalyst	Conversion [%][a]
1	**5**	0
2	**6**	8
3	**7**	15
4	**8**	30
5	**9**	35
6	**10**	95
7	**11**	8
8	**12**	0

[a] Determined by gas chromatography.



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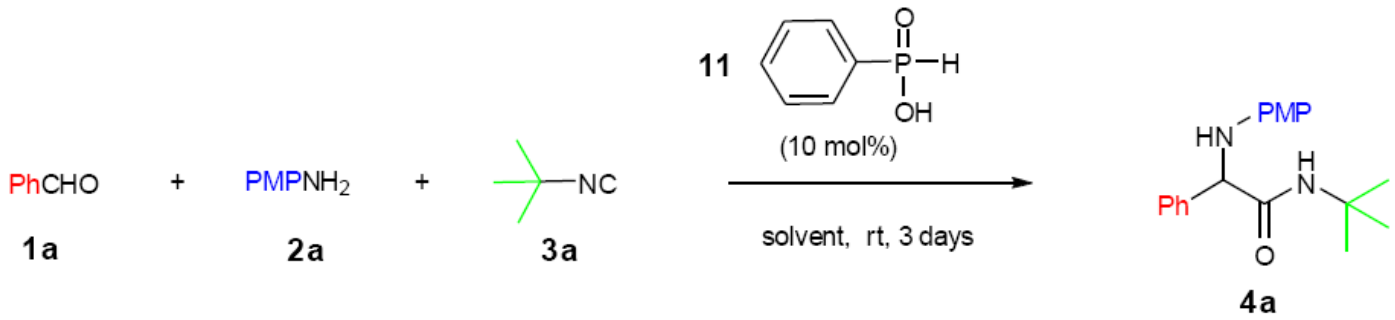
Catalytic Three-Component Ugi Reaction : Solvent Study



Solvent	Conv. (GC)
CH_2Cl_2	95
toluene	96
CH_3CN	85
benzene	94
$CHCl_3$	92
1,4-dioxane	89
DMF	89
DMSO	93
CF_3CH_2OH	52
MeOH	30

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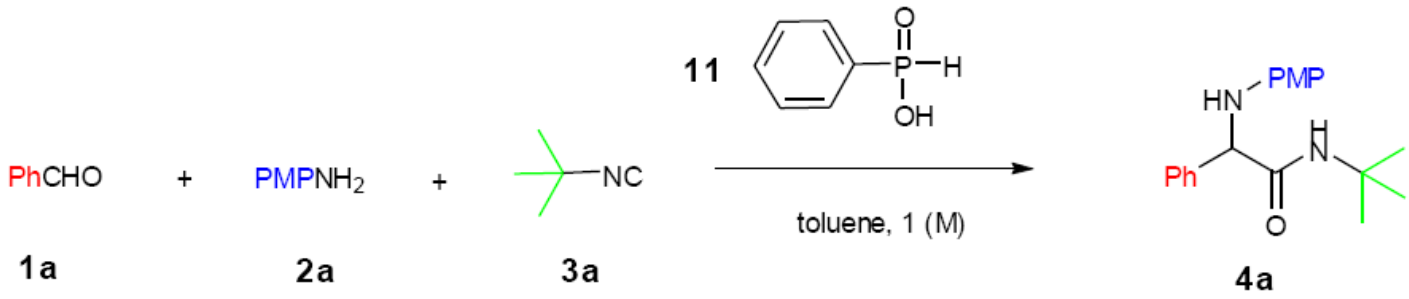
Catalytic Three-Component Ugi Reaction : Temperature Study



Catalyst (Mol%)	Temp (°C)	Time	GC Conv.
10	50	24h	95
5	50	48h	78
1	50	48h	51
0	50	48h	0
10	80	12h	95
5	80	24h	83

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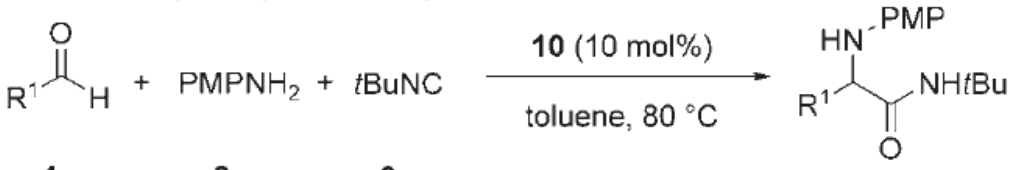
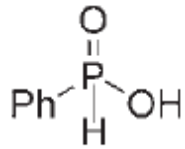
Catalytic Three-Component Ugi Reaction: Substrate Scope

Table 2: Catalytic three-component Ugi reaction of different aldehydes with *tert*-butyl isocyanide and *p*-anisidine.



1 **2a** **3a** **4**



10

Entry[a]	R^1	Product	Time [h]	Yield [%][b]
1	Ph	**4a**	12	91
2	4-$MeOC_6H_4$	**4b**	12	88
3	4-ClC_6H_4	**4c**	20	78
4	2-ClC_6H_4	**4d**	20	82
5	2-naphthyl	**4e**	20	87
6[c]	(*E*)-CH=CHPh	**4f**	20	83
7	3-pyridyl	**4g**	20	51
8	*i*Pr	**4h**	20	74
9	*c*Hex	**4i**	20	81
10	*t*Bu	**4j**	20	52
11	*n*Bu	**4k**	20	61

[a] Reaction conditions: Aldehyde **1** (0.5 mmol), *p*-anisidine (**2a**, 0.5 mmol), *tert*-butyl isocyanide (**3a**, 0.5 mmol), and catalyst **10** (0.05 mmol) were stirred at 80 °C in toluene (0.5 mL). [b] Yield of the product after silica gel column chromatography. [c] Using 20 mol% of catalyst **10**.

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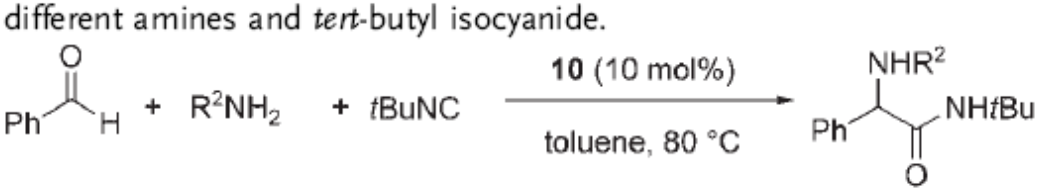
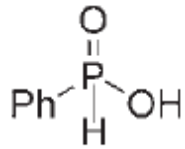
Catalytic Three-Component Ugi Reaction: Substrate Scope

Table 3: Catalytic three-component Ugi reaction of benzaldehyde with different amines and *tert*-butyl isocyanide.



1a **2** **3a** **4**



10

Entry[a]	R^2	Product	Time [h]	Yield [%][b]
1	2-naphthyl	**4l**	20	83
2	4-$CF_3C_6H_4$	**4m**	20	81
3	4-$CO_2EtC_6H_4$	**4n**	20	88
4	3-ClC_6H_4	**4o**	20	74
5	3-pyridyl	**4p**	20	81
6	$PhCH_2$	**4q**	20	42
7[c]	$(Ph)_2CH$	**4r**	36	36
8	Allyl	**4s**	20	40
9	$R^2{}_2NH$=$(Ph)_2NH$	**4t**	36	41

[a] Reaction conditions analogous to those described in Table 2. [b] Yield of the product after silica gel column chromatography. [c] Using 20 mol % of catalyst **10**.

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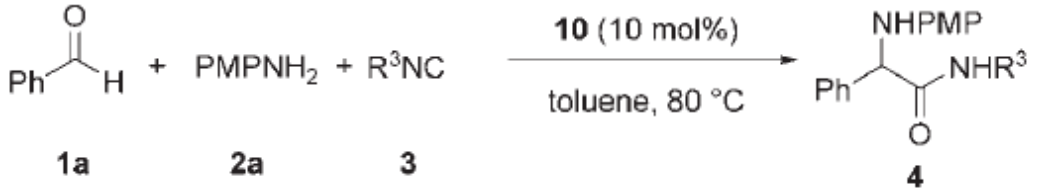
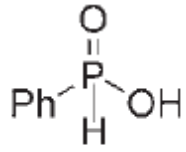
Catalytic Three-Component Ugi Reaction: Substrate Scope

Table 4: Catalytic three-component Ugi reaction of benzaldehyde with *p*-anisidine and different isocyanides.



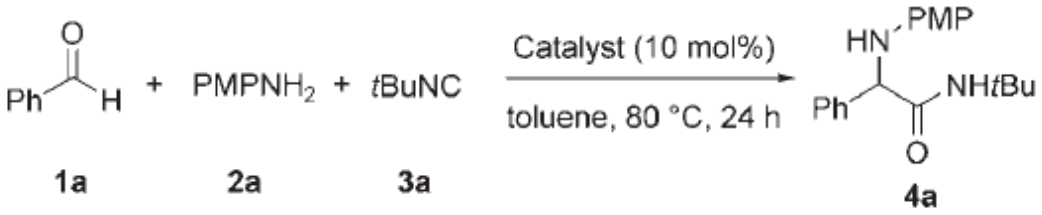
1a **2a** **3** **4**



10

Entry[a]	R^3	Product	Time [h]	Yield [%][b]
1	*c*Hex	**4u**	20	78
2	Bn	**4v**	36	64
3	*t*Bu$CH_2C(Me_2)$	**4w**	20	62
4	EtO_2CCH_2	**4x**	20	83
5	*p*TsCH_2	**4y**	20	68

[a] Reaction conditions analogous to those described in Table 2. [b] Yield of the product after silica gel column chromatography.



1a **2a** **3a** **4a**

Catalyst	Yield	*ee*
TRIP	15 %	18 %
Chiral phosphinic acid	90%	04 %

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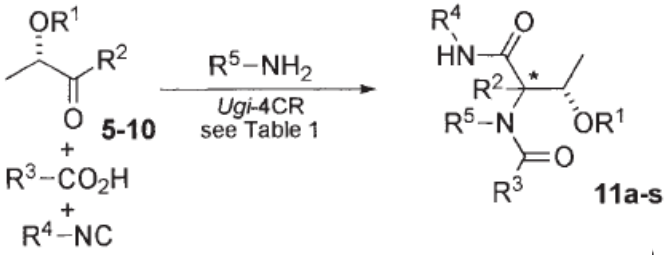
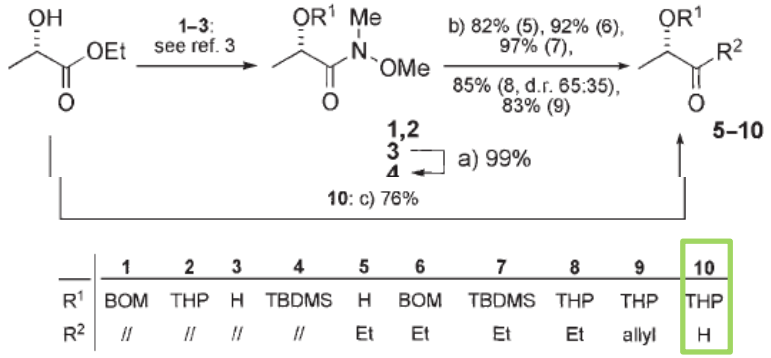
Synthesis of Aziridines *via* Ugi Reaction





	1	2	3	4	5	6	7	8	9	10
R^1	BOM	THP	H	TBDMS	H	BOM	TBDMS	THP	THP	THP
R^2	//	//	//	//	Et	Et	Et	Et	allyl	H

Scheme 1. a) TBDMS-Cl, imidazole, Dimethyl Formamide (DMF), rt; b) EtMgBr (**5**,**6**,**7**,**8**) or allylMgBr (**9**), Tetrahydrofuran (THF), −78 °C; c) DIBALH, *n*-hexane, −80 °C.

Entry[a]	Carbonyl compound	R^3	R^4	R^5	Time	Product	Yield[b]
1	**5**	Et	*n*Bu	Bn	2 d	**11a**	//[c]
2	**6**	Et	*n*Bu	Bn	24 h	**11b**	84%
3	**6**	Et	(4-OMe)-C_6H_4	Bn	1.5 d	**11c**	31% (38%)[d]
4	**7**	Et	*n*Bu	Bn	2 d	**11d**	87%
5	**7**	Et	*n*Bu	*n*Bu	23 h	**11e**	53%
6	**7**	Et	*n*Bu	$Ph(CH_2)_2$	4 d	**11f**	68%
7	**7**	Et	Bn	*n*Bu	2 d	**11g**	65%
8	**7**	Ph	*n*Bu	Bn	7 d	**11h**	58%
9	**7**	Et	*n*Bu	none	2 d	**12a**	70%
10	**8**	Et	*n*Bu	Bn	1.8 d	**11i**	93%
11	**8**	Et	*n*Bu	allyl	2.4 d	**11j**	72%
12	**8**	Et	*n*Bu	2,4-DMB	5 d	**11k**	30%
13	**8**	Et	*n*Bu	$Ph(CH_2)_2$	2 d	**11l**	31% (42%)[d]
14	**8**	Et	*t*Bu	Bn	2 d	**11m**	59%
15	**8**	Et	Cy	Bn	1.5 d	**11n**	66%
16	**8**	Et	(4-OMe)-C_6H_4	Bn	1.8 d	**11o**	50% (64%)[d]
17	**8**	Me	*n*Bu	Bn	3 d	**11p**	64%
18	**8**	H	*n*Bu	Bn	2 d	**11q**	//[e]
19	**8**	Et	*n*Bu	none	7 d	**12b**	77%
20	**9**	Et	*n*Bu	Bn	2 d	**11r**	//[c,f]
21	**10**	Et	*n*Bu	Bn	2 h	**11s**	73%

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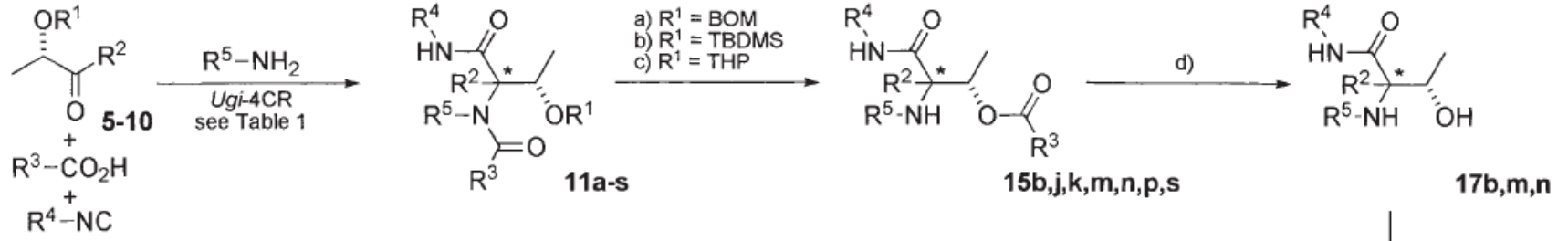
Synthesis of Aziridines *via* Ugi Reaction

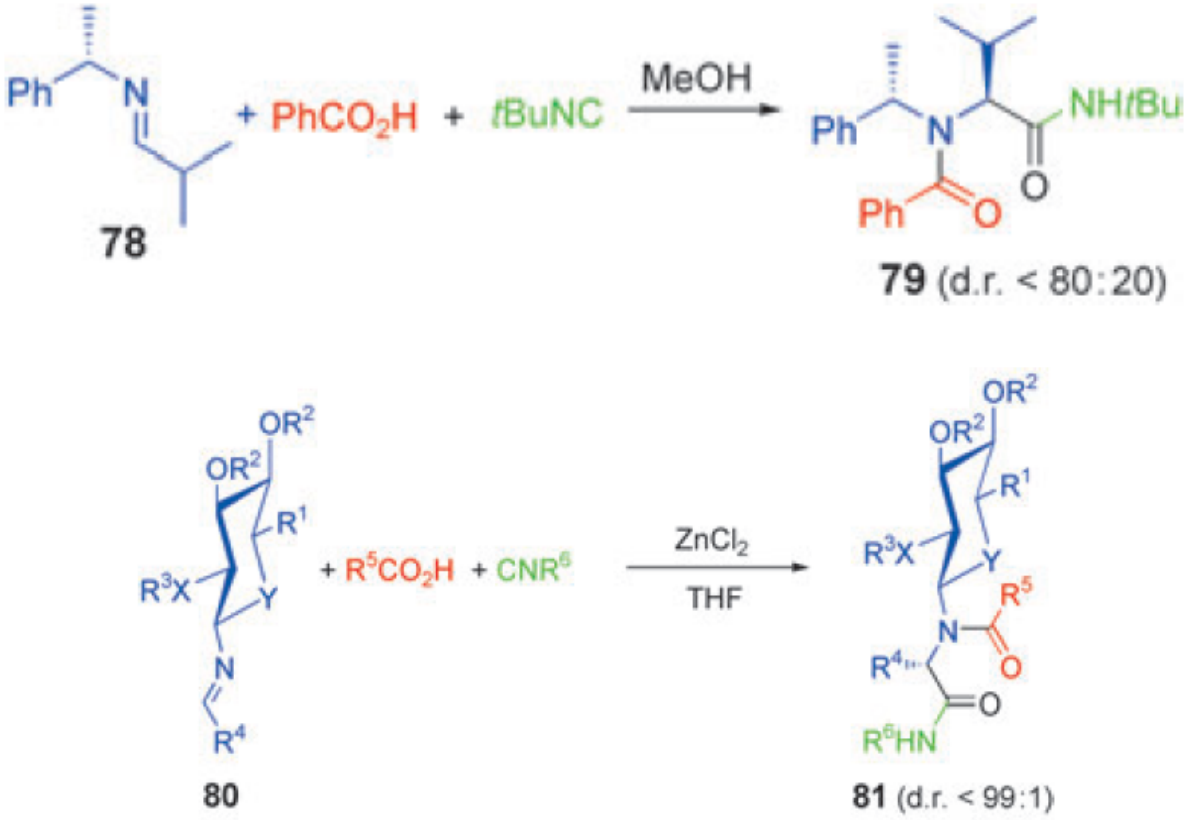


Entry	Start. comp.	R^4	R^5	Yield[a] [15 or 16]	Yield [17]	Yield [19]
1	**11b**	*n*Bu	Bn	54%[b,c]		
2	**11d**	*n*Bu	Bn	50%[b,d]	90–93%	62–70%
3	**11i**	*n*Bu	Bn	43%[b,c,e]		
4	**11j**	*n*Bu	allyl	33%[e]	//	
5	**11k**	*n*Bu	2,4-DMB	36%[e]	//	
6	**11m**	*t*Bu	Bn	42%[e]	88%	74%
7	**11n**	Cy	Bn	54%[e]	80–86%	60–76%
8	**11p**	*n*Bu	Bn	28%[e]	//	
9	**11s**	*n*Bu	Bn	31%[g]	//	
10	**12b**	*n*Bu	none	80%[e]	//	

Scheme 2. a) H_2, Pd/C, EtOH/AcOH 96:4, rt; b) camphorsulfonic acid, MeOH, rt; c) HCO_2H/THF/H_2O 3:2:1 or HCO_2H/MeOH/H_2O 3:1:1, 45°; d) KOH, MeOH, rt; e) MsCl, Et_3N, CH_2Cl_2, −30° → rt.

Banfi, L.; Basso, A.; Guanti, G.; Paravidino, M.; Riva, R *QSAR Comb.Sci*. *25*, **2006**, 457

Diastereoselective Ugi Reaction (3CR): Chiral Imines



Ugi, K. Offeremann, H. Herlinger, D. Marquarding, *Justus Liebigs Ann. Chem.* **1967**, 1.

S. Lehnhoff, M. Goebel, R. M. Karl, R. Klsel, I. Ugi, *Angew. Chem. Int. Ed.* **1995**, *34*, 1104.