Mild and Selective Hydrozirconation of Amides to Aldehydes Using $Cp_2Zr(H)Cl$: Scope and Mechanistic Insight

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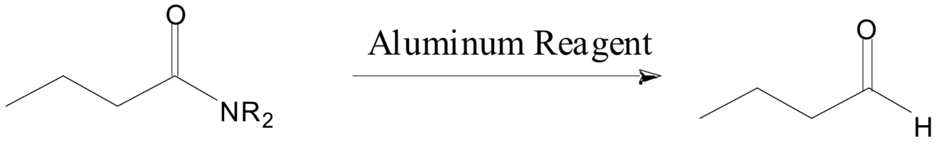
J. Am. Chem. Soc. ASAP Article

David Arnold: 3/3/07

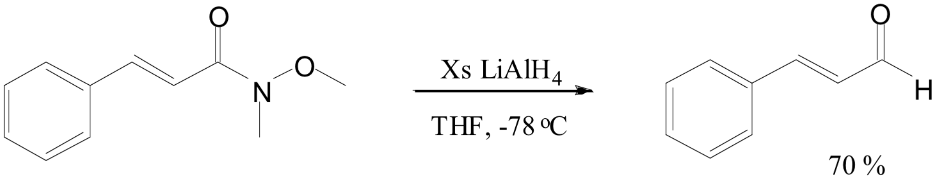
Brief Background



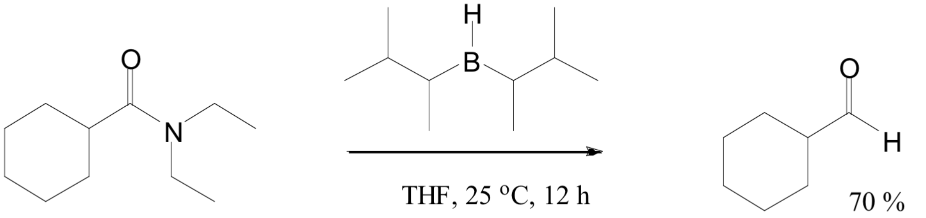
NR_2	$LiAlH_4$	$Li(OEt)_3AlH$
Me	25%	85%
Aziridine	88%	87%
Isopropyl	NR	NR

- Over reduction
- Sensitive to steric effects
- Chemoselectivity?

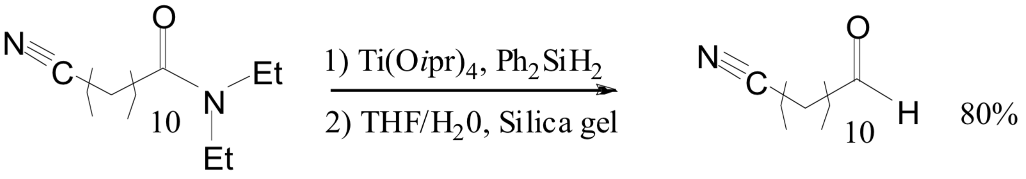
J. Am. Chem. Soc. **1961**, *83*, 4549.
J. Am. Chem. Soc. **1964**, *86*, 1089.



- Decrease in over reduction
- Increased chemoselectivity
  Tetrahedron Lett. **1981**, *22*, 3815.



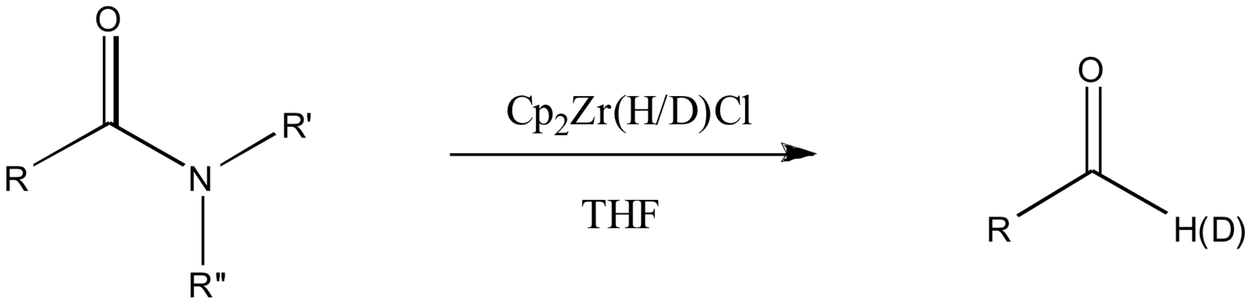
- Moderate to excellent yields
- No observed over reduction
- Chemoselectivity?
  Tetrahedron Lett. **1997**, *38*, 1717.



- Good yields
- Good Chemoselectivity - Olefins, Alkynes, Nitriles and Epoxides
- Limited to α-enolizable amides

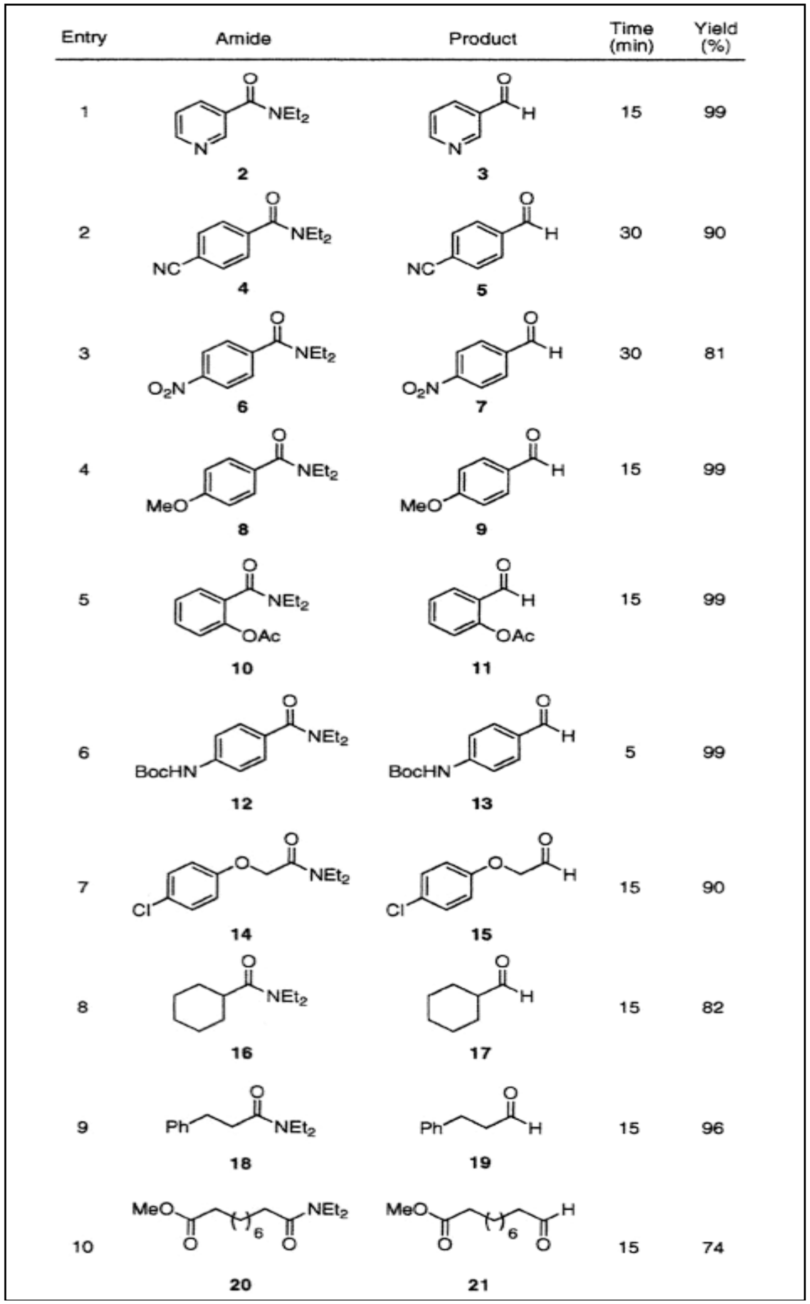
Angew. Chem. Int. Ed. Eng. **1996**, *35*, 1515.

Author’s Work



- Scope
- Utility
- Mechanism

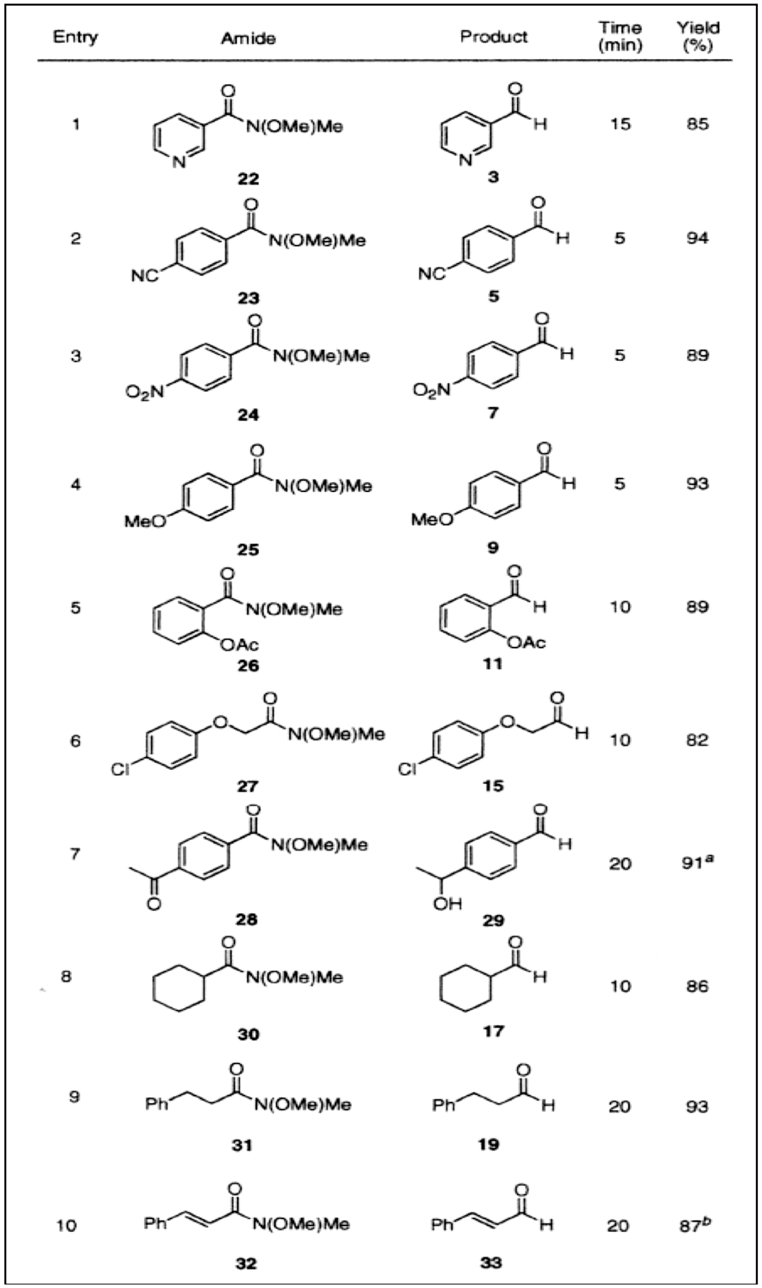
Reduction of N,N-Dialkyl Amides



Entry	Amide	Product	Time (min)	Yield (%)
1	2	3	15	99
2	4	5	30	90
3	6	7	30	81
4	8	9	15	99
5	10	11	15	99
6	12	13	5	99
7	14	15	15	90
8	16	17	15	82
9	18	19	15	96
10	20	21	15	74

- Short reaction times
- Good to excellent yields
- Amides:
  - Aromatic
  - Heteroaromatic
  - Aliphatic
- Chemoselectivity:
  - Nitrile
  - Nitro
  - Ester
  - Carbamate

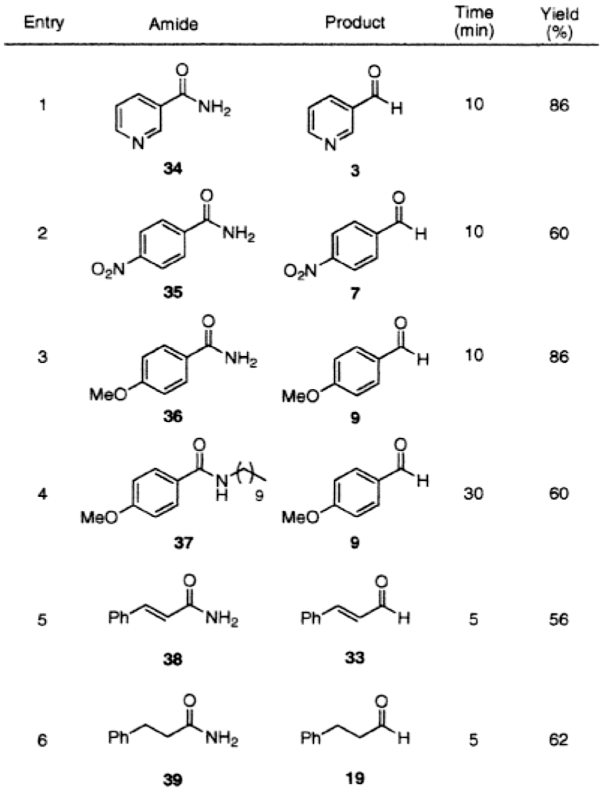
Reduction of Weinreb Amides



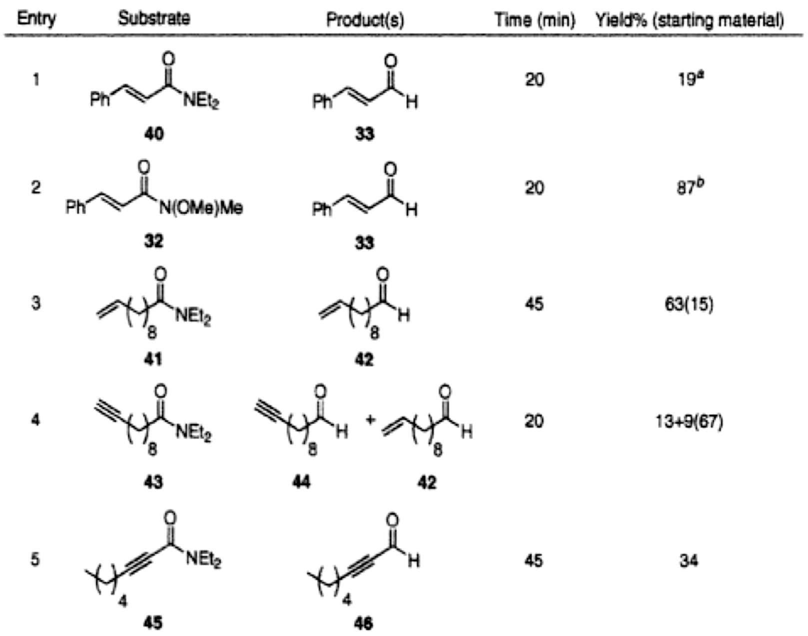
Entry	Amide	Product	Time (min)	Yield (%)
1	**22**	**3**	15	85
2	**23**	**5**	5	94
3	**24**	**7**	5	89
4	**25**	**9**	5	93
5	**26**	**11**	10	89
6	**27**	**15**	10	82
7	**28**	**29**	20	91[a]
8	**30**	**17**	10	86
9	**31**	**19**	20	93
10	**32**	**33**	20	87[b]

- Similar yields and reaction times
- Chemoselectivity maintained

Reduction of Primary, Secondary, Alkenyl and Alkynyl Amides



Entry	Amide	Product	Time (min)	Yield (%)
1	**34**	**3**	10	86
2	**35**	**7**	10	60
3	**36**	**9**	10	86
4	**37**	**9**	30	60
5	**38**	**33**	5	56
6	**39**	**19**	5	62



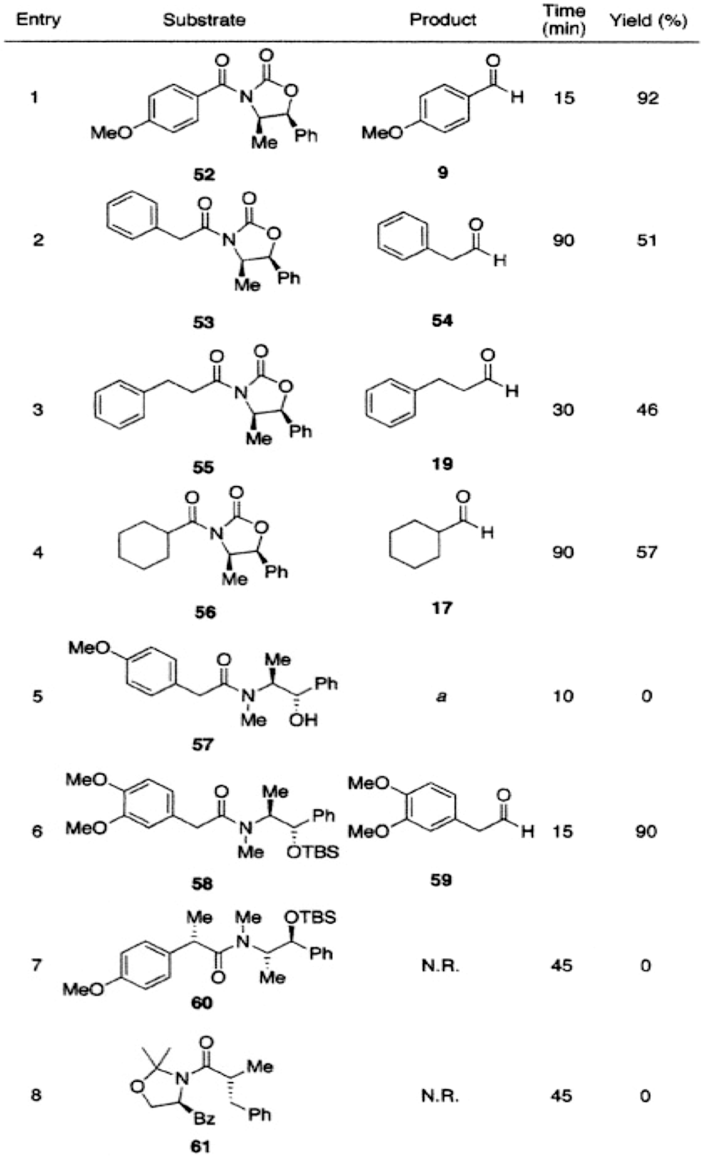
Entry	Substrate	Product(s)	Time (min)	Yield% (starting material)
1	**40**	**33**	20	19[a]
2	**32**	**33**	20	87[b]
3	**41**	**42**	45	63(15)
4	**43**	**44** + **42**	20	13+9(67)
5	**45**	**46**	45	34

- Similar reaction times
- Significantly reduced yields
- Chemoselectivity maintained

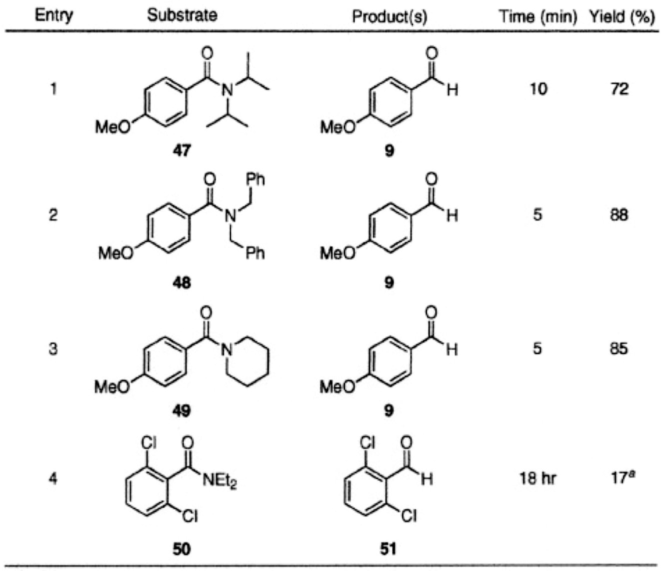
Chemoselectivity:

- Good for conjugated internal and terminal olefins
- Poor for external alkynes

Effects of Steric Bulk and Reduction of Amides Containing Chiral Auxiliaries



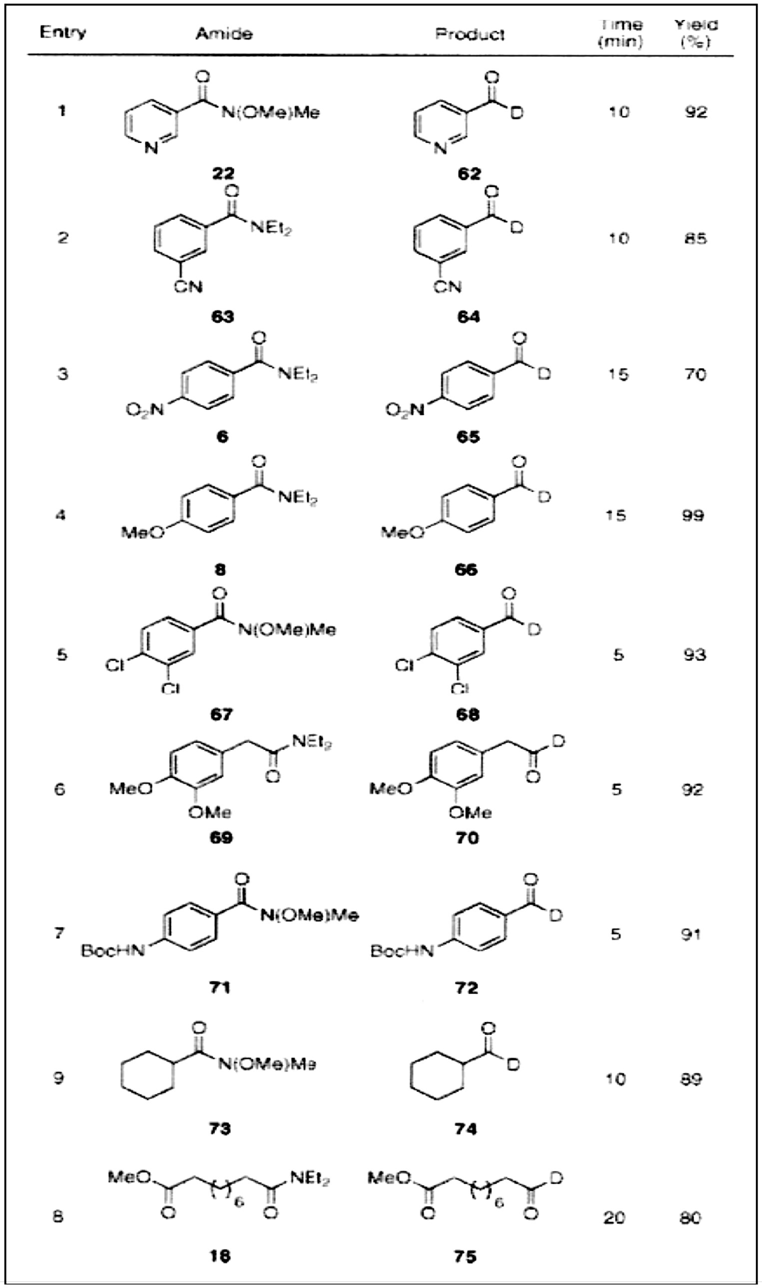
Entry	Substrate	Product	Time (min)	Yield (%)
1	52	9	15	92
2	53	54	90	51
3	55	19	30	46
4	56	17	90	57
5	57	*a*	10	0
6	58	59	15	90
7	60	N.R.	45	0
8	61	N.R.	45	0



Entry	Substrate	Product(s)	Time (min)	Yield (%)
1	47	9	10	72
2	48	9	5	88
3	49	9	5	85
4	50	51	18 hr	17[a]

- Steric bulk tolerated on amine side
- Evans oxazolidinone removed in moderate yields with an α-methylene / methine carbon
- Myers auxiliary removed in good yield with alcohol protection
- α substitution hinders hydrozirconation

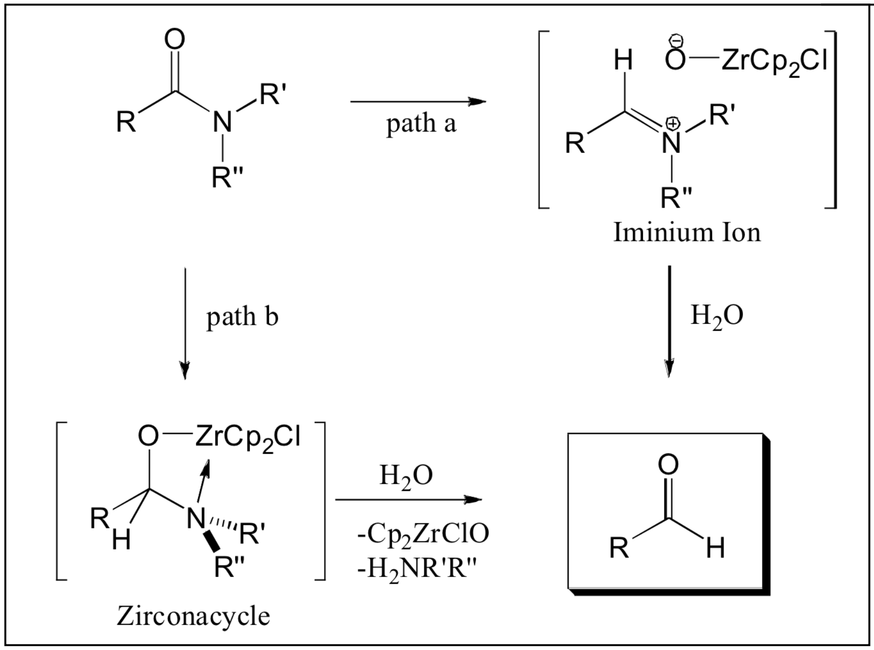
Amide Reduction Using $Cp_2Zr(D)Cl$



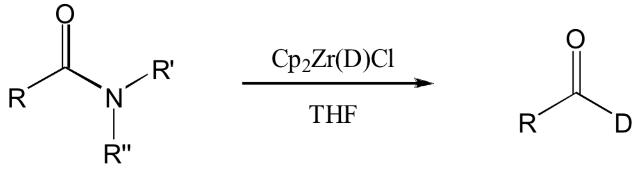
Entry	Amide	Product	Time (min)	Yield (%)
1	**22**	**62**	10	92
2	**63**	**64**	10	85
3	**6**	**65**	15	70
4	**8**	**66**	15	99
5	**67**	**68**	5	93
6	**69**	**70**	5	92
7	**71**	**72**	5	91
9	**73**	**74**	10	89
8	**18**	**75**	20	80

- Mild reaction conditions
- Good yields
- Chemoselectivity
- $\geq$ 95% deuterium incorporation

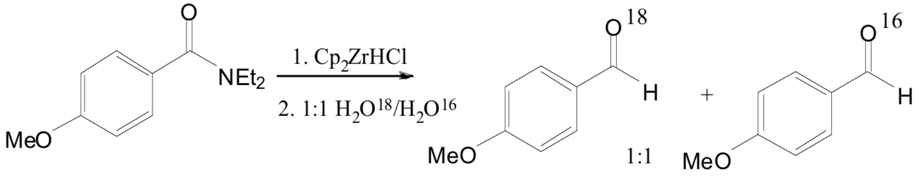
Mechanistic Insight: Intermediate Structure Determination



1. Source of Hydride:

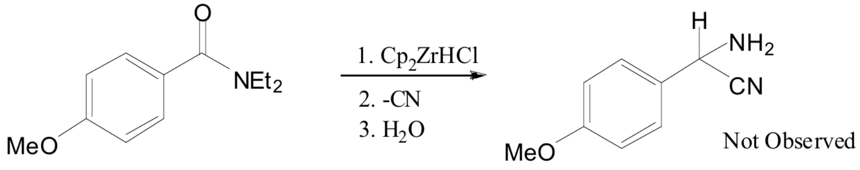


2. Source of Aldehyde Carbonyl Oxygen:

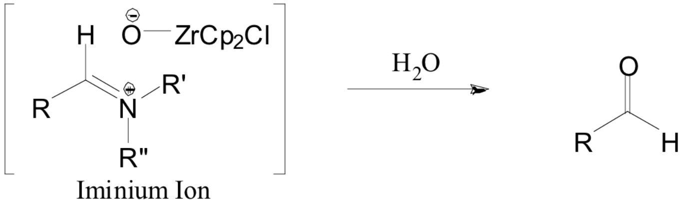


Ratios found by ^{13}C NMR and MS

3. Chemical evidence for the Iminium ion?



4. IR analysis of the Intermediate:



- No distinctive Imminium Ion Stretch
- Formation of a carbonyl peak at 1699 cm^{-1} after Hydrolysis

5. Attempted Crystallization of the Intermediate:

$$ClCp_2Zr—O—ZrCp_2Cl$$

Strong Support for the Zirconacycle Intermediate from NMR

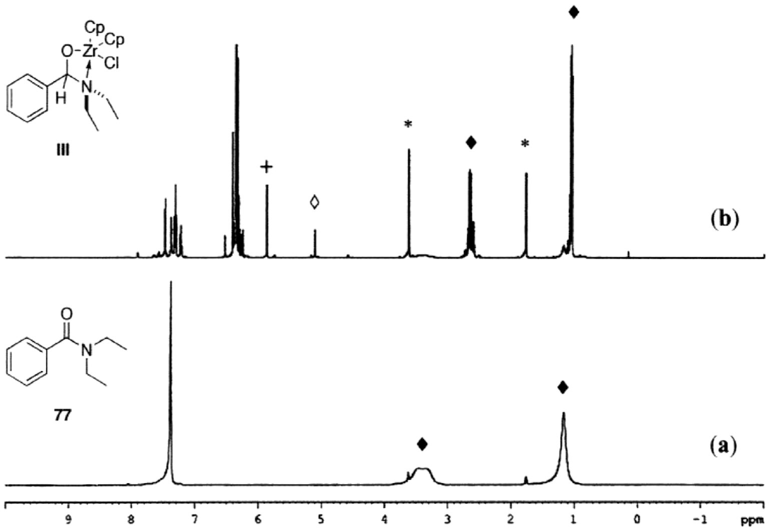


Figure 1. ^{1}H NMR spectra of reaction intermediate **III**: (♦) denotes $-CH_2-$ and $-CH_3$ peaks, (*) residual THF signals, (+) methine proton, (◊) minor product.

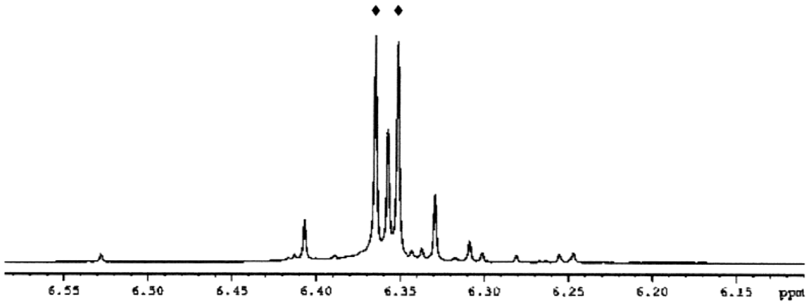
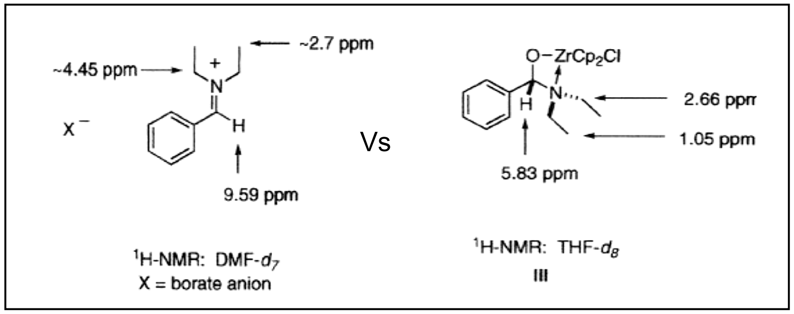


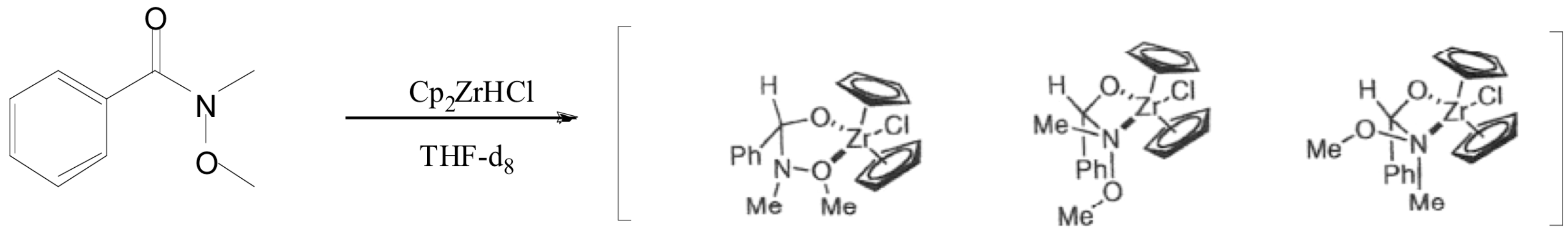
Figure 2. Expansion of Cp region for intermediate **III**: (♦) denotes diastereotopic Cp resonances.



- Rotameric diethyl peaks resolve and shift upfield
- Methine proton appears at 5.83 ppm
- Methine Carbon appears at 97 ppm
- Diasterotopic splitting of the Cp groups is observed
- A ^{13}C enriched sample of the duterated analogue showed:

1. A loss of the methine proton in ^{1}H NMR
2. Formation of the methine peak in ^{2}H NMR
3. A triplet at 97 ppm in ^{13}C NMR

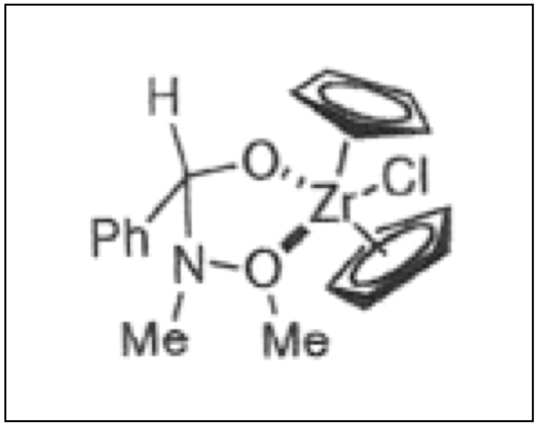
NMR Evidence for the Structure of a Similar Weinreb Amide Derived Intermediate



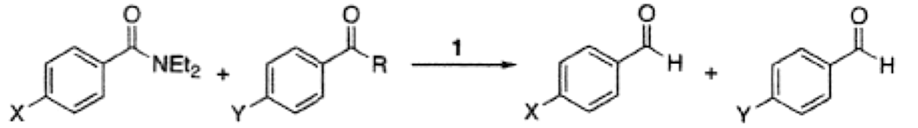
Possible intermediate species

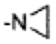
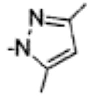
- 1H NMR:
  Single set of Methyl Peaks upfield from the starting amide

- 2D-NOSEY:
  No correlation between the methine proton with any other protons in the molecule



Pre-Intermediate Formation: Competition Studies



Entry	X	Y	R	ratio of X:Y[a]	IR stretch of RCO cm^{-1}
1	-OMe	-NO$_2$	-NEt$_2$	1:1	1622
2	-OEt	-OMe	-NEt$_2$	1:1.1	1625
3	-OEt	-OMe		22:1	1635
4	-OEt	-OMe		19:1	1683

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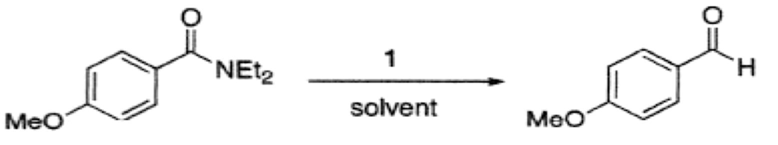
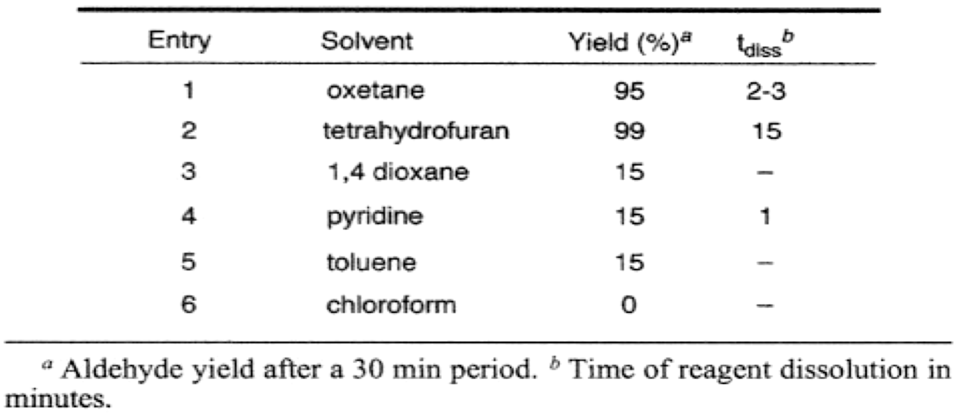
[a] Determined by ^{1}H NMR spectroscopy, average of two runs.

- Differences in electronic substitution on the carbonyl side have little effect on kinetic selectivity.

- Increased carbonyl electron density from the amide lone pair favors hydrozirconation.

Solvent Effects





Entry	Solvent	Yield (%)[a]	t_{diss}[b]
1	oxetane	95	2-3
2	tetrahydrofuran	99	15
3	1,4 dioxane	15	–
4	pyridine	15	1
5	toluene	15	–
6	chloroform	0	–

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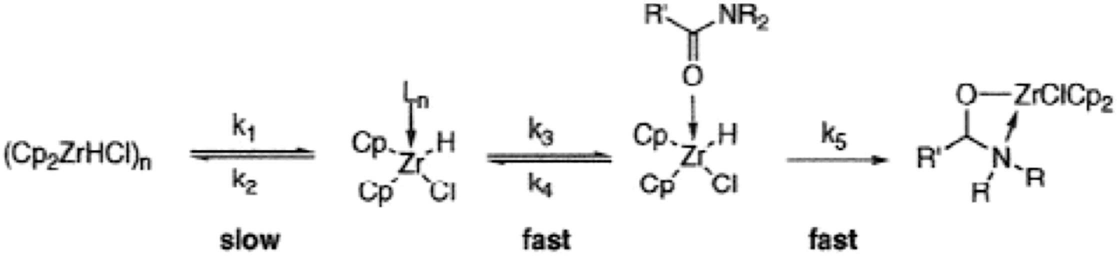
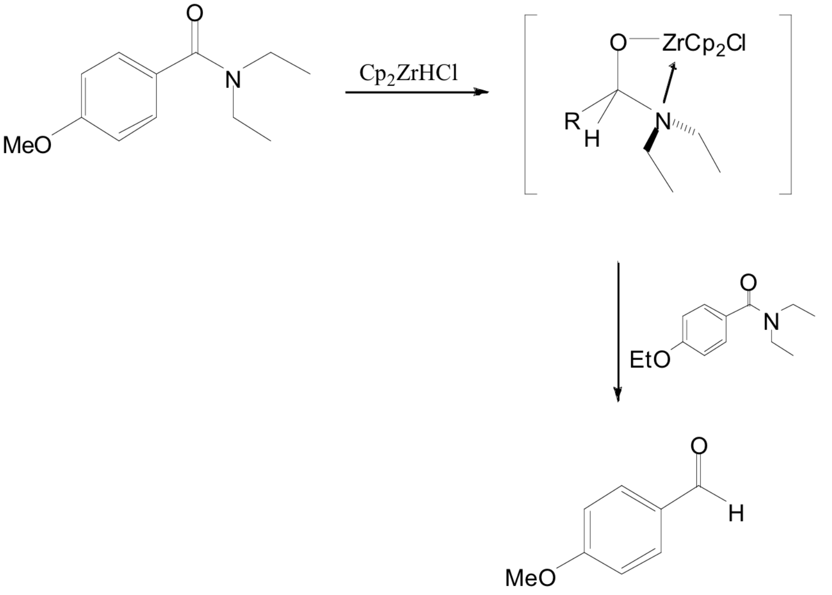
[a] Aldehyde yield after a 30 min period. [b] Time of reagent dissolution in minutes.

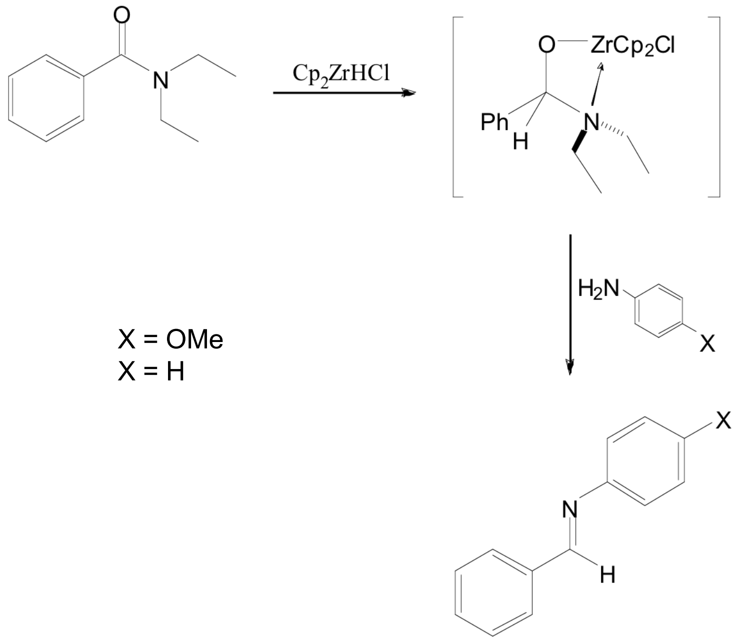


- t_{diss} = Time it takes for the solution to clear

Irreversible Migratory Insertion and The Conversion of the Zirconacycle Intermediate to Imines



- p-methoxybenzaldehyde is the only product observed by ^{1}H NMR and HPLC after 1.5 h.
- Strong evidence that the migratory insertion event is irreversible for amides.



X = OMe
X = H

- Demonstrates that tertiary amides can act as a robust precursor to both aldehydes and aldimines.

Conclusion

- The authors have reported a convenient methodology which utilizes Schwartz's reagent to convert tertiary amides to aldehydes. The benefits of this methodology include:

  - Fast Reaction Times
  - Overall Good Yields
  - Broad Scope and Synthetic Utility
  - Good Chemoselectivity

- The author have also given good insight into the mechanism of this reaction through the characterization of two stable intermediates, which helps to broaden our understanding of how Schwartz's reagent works.