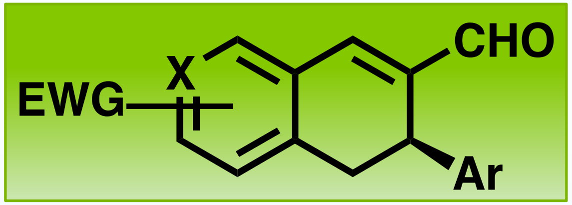
FORMATION OF DIHYDRONAPHTHALENES VIA ORGANOCATALYTIC ENANTIOSELECTIVE MICHAEL-ALDOL CASCADE REACTIONS WITH ARYLALKANES

Xiangmin, L.; Sinan, W.; Tengfei, L.; Jian, L.; Hao, L. And Wei, W.
***Org. Lett.* 2013** 10.1021/ol402489e



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November 4 of 2013

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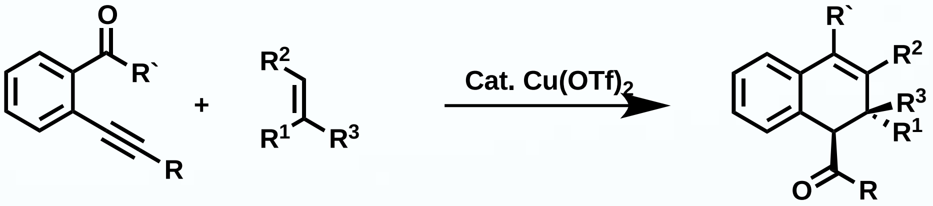
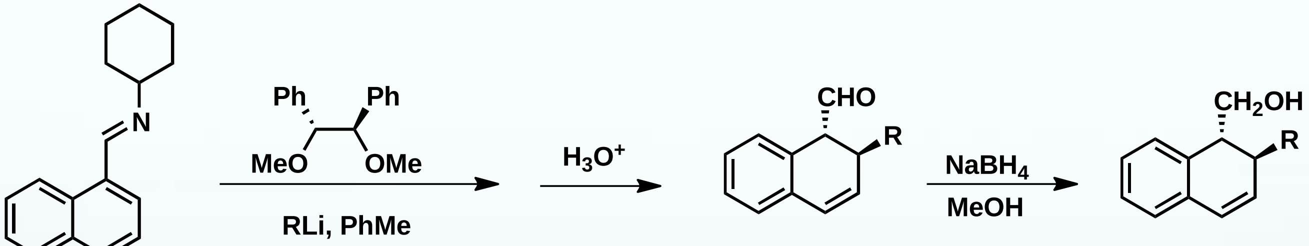
UMR 7313

SYNTHETIC METHODS FOR DIHYDRONAPHTHALENES



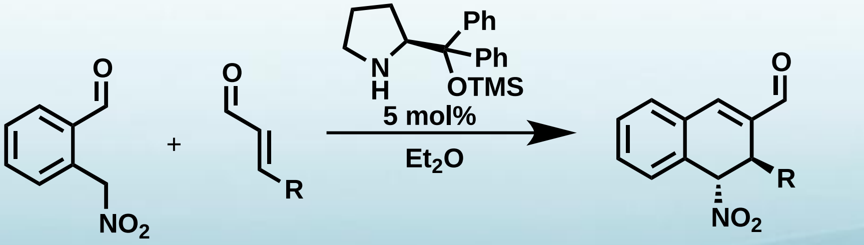
Angew. Chem. Int. Ed. **2003,** *42*, 3504

Asymmetric strategies



ee: up 90%

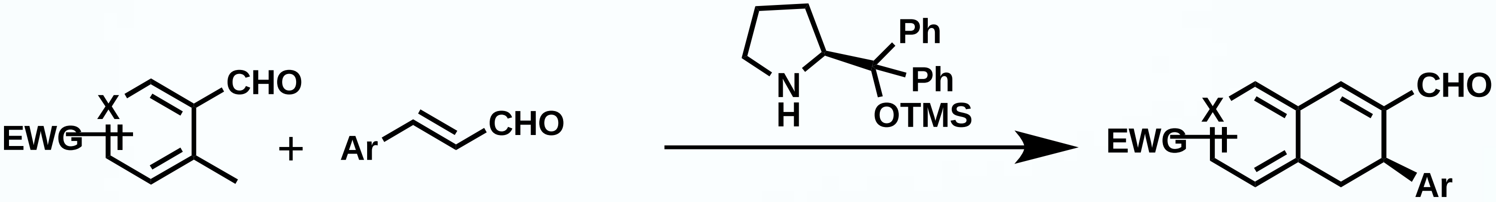
J. Am. Chem. Soc. **1989,** *111*, 8266



Synlett. **2009**, *11*, 1777

ee: up 91%

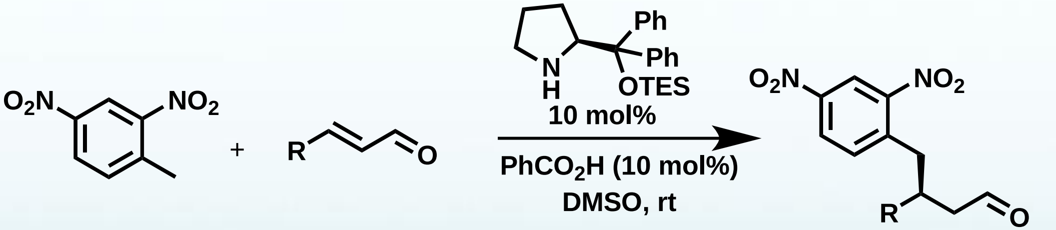
DIHYDRONAPHTHALENES VIA MICHAEL-ALDOL CASDADE REACTION



X= C,N

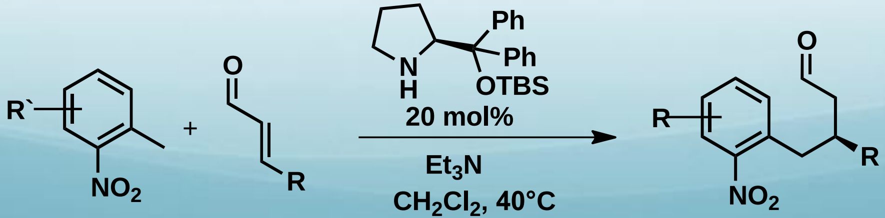
- The very weak nucleophilicity of the benzene-tethered methyl group renders it impossible to perform a conjugate addition under mild contidions.

Previous strategies to activate the methyl group



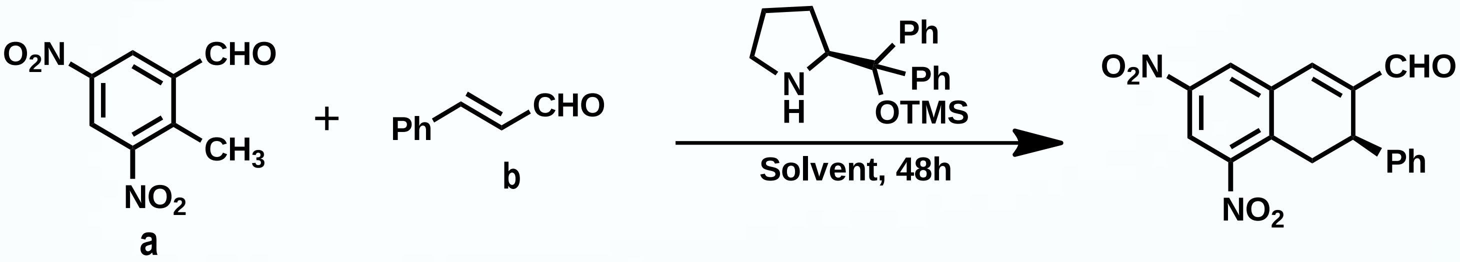
Chem. Eur. J. **2013**, *19*, 9147

- The nitro group on aromatc ring thereby rendering the methyl group hydrogen acidic.



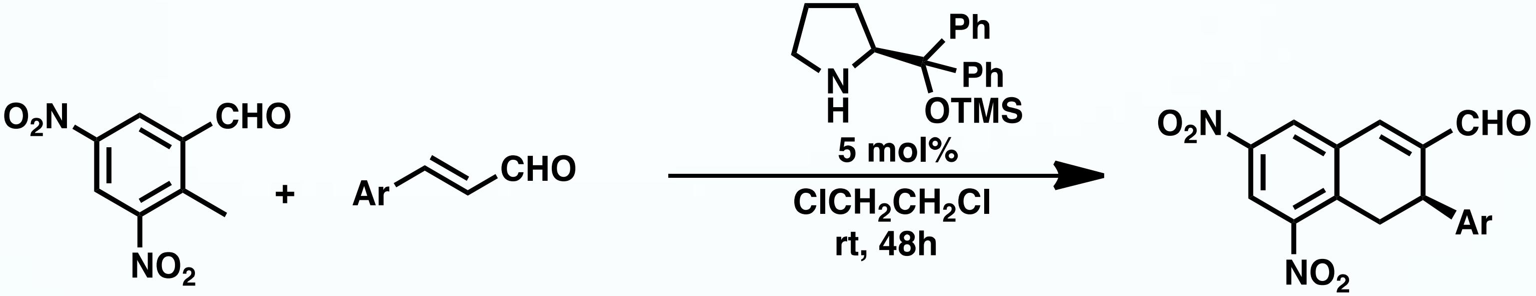
Eur. J. Org. Chem. **2013**, 5262

OPTIMIZATION OF REACTION CONDITIONS



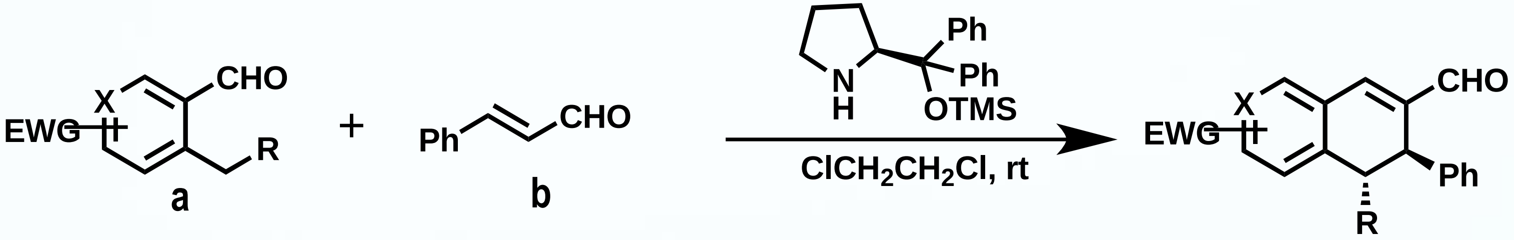
Entry	Solvent	Ratio (a/b)	Cat. Loading (mol %)	Yield (%)	ee (%)
1	CH_2Cl_2	1	20	36	95
2	$ClCH_2CH_2Cl$	1	20	48	99
3	THF	1	20	45	99
4	toluene	1	20	12	99
5	CH3CN	1	20	23	99
6	DMF	1	20	0	--
7	DMSO	1	20	0	--
8	$ClCH_2CH_2Cl$	1.2	20	54	99
9	$ClCH_2CH_2Cl$	1.5	20	61	99
10	$ClCH_2CH_2Cl$	1.5	10	68	99
11	$ClCH_2CH_2Cl$	1.5	5	72	99
12	$ClCH_2CH_2Cl$	1.5	5	79	99
13	**$ClCH_2CH_2Cl$**	**2.0**	**5**	**83**	**99**

SCOPE OF REACTION WITH DIFFERENT α,β-UNSATURATED ALDEHYDES

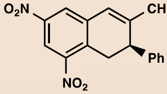
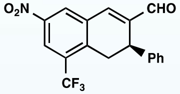
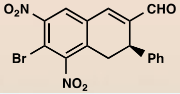
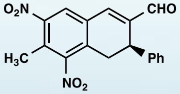
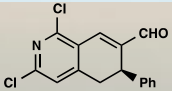
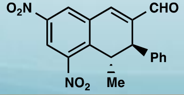


Entry	Ar	Yield (%)	ee (%)
1	C_6H_5	83	99
2	2-MeOC_6H_4	96	97
3	4-MeOC_6H_4	93	97
4	2-MeC_6H_4	86	99
5	4-MeC_6H_4	80	97
6	2-ClC_6H_4	81	98
7	4-ClC_6H_4	78	99
8	3-FC_6H_4	70	91
9	3$CF_3C_6H_4$	77	97
10	3-BrC_6H_4	72	92
11	3-MeO-4-AcOC_6H_3	72	96
12	2-furanyl	73	92

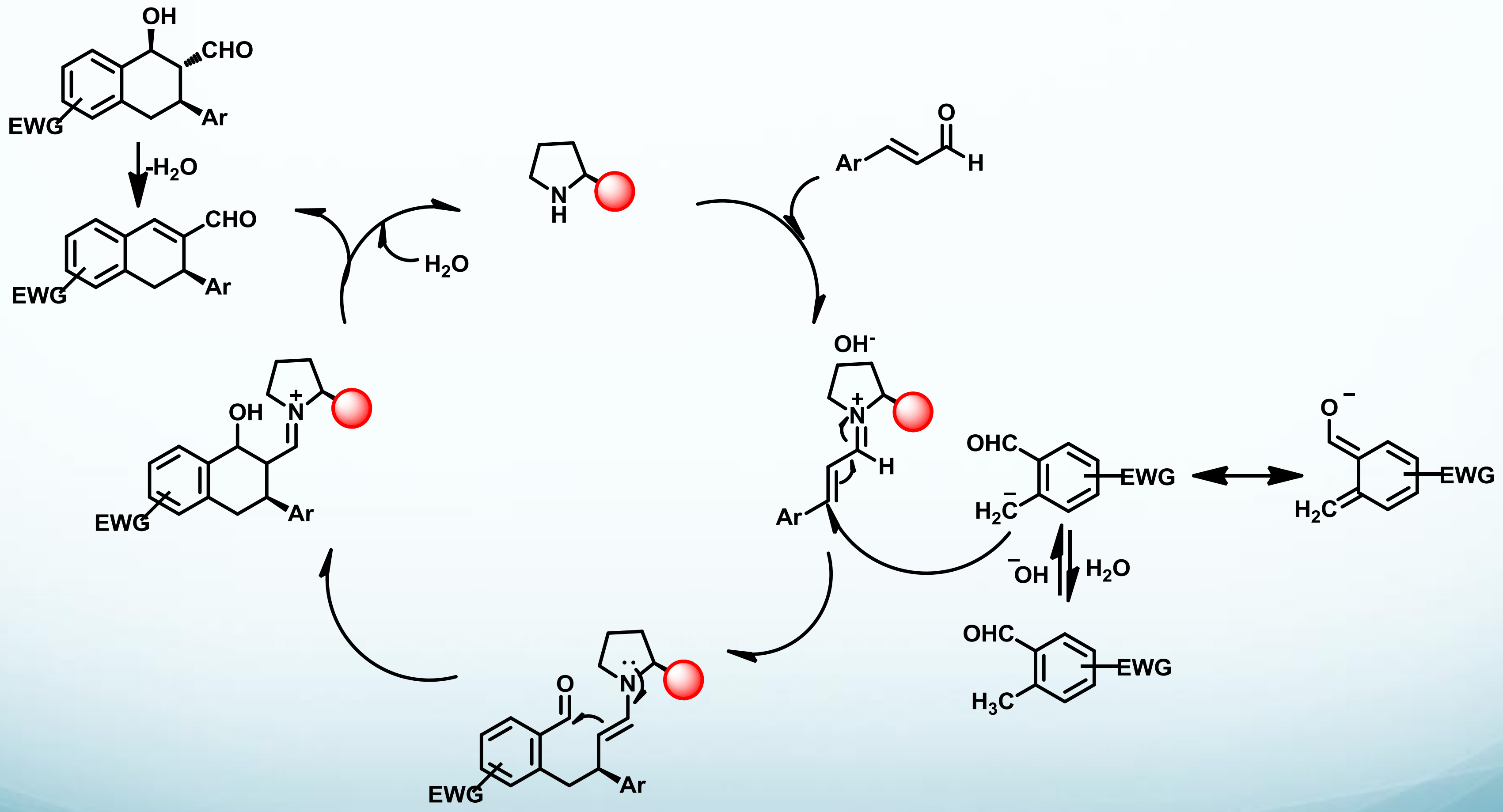
STRUCTURAL ALTERNATION OF THE SUBSTRATES a



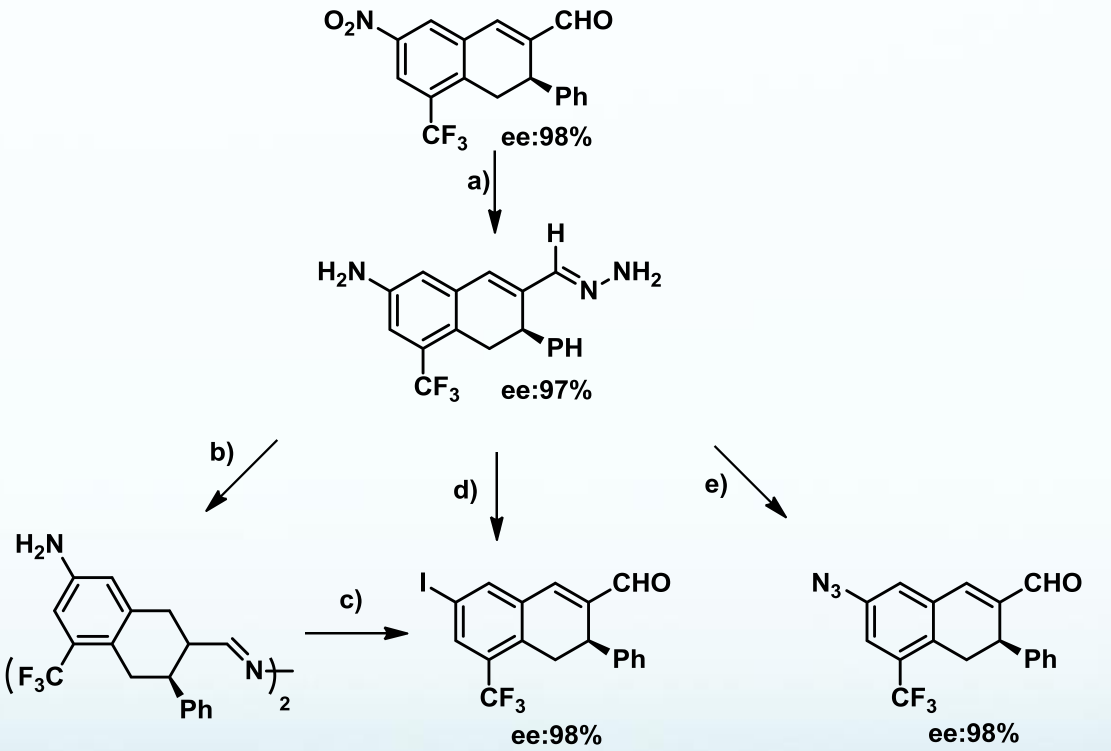
X= C,N

Entry	Ar	Cat. Loading (mol %)	t (h)	Yield (%)	ee (%)
1		5	48	83	99
2		20	48	96	97
3		20	48	93	97
4		30	48	86	99
5		30	24	80	97
6		30	72	81	98

PROPOSED MECHANISM FOR THE MICHAEL-ALDOL CASCADE REACTION



TRANSFORMATIONS OF THE NITRO GROUP TO NEW FUNCTIONALITIES



a) Pd/C $N_2H_4.H_2O$, EtOH, reflux, 100% yield

b) HCl, THF: H_2O = 1:1, NaOH, 98% yield

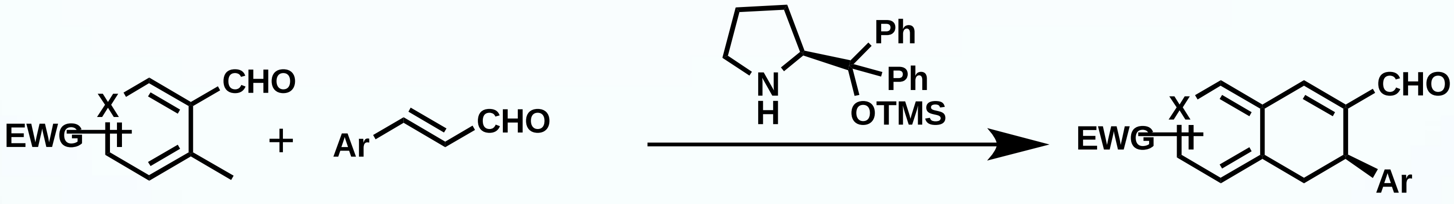
c) $NaNO_2$, HCl, KI, H_2O 0 ºC to 90 ºC, 83%yield

d) $NaNO_2$, HCl, KI, H_2O 0 ºC to 90 ºC, 50%yield

e) $NaNO_2$, HCl, H_2O, 50 ºC, 85%yield

CONCLUSIONS

- Wang and co-worker developed a new organocatalytic highly enantioselective nucleophilic carbon initiated Michael-aldol cascade reaction for "one pot" construction of valuable chiral dihydronaphthalenes.



- This process is the first time, that aryl methyl nucleophiles are explored under mild reaction conditions in a cascade manner.

THANKS