Enantioselective [4 + 2]-Annulation of Oxadienes and Allenones Catalyzed by an Amino Acid Derived Phosphine: Synthesis of Functionalized Dihydropyrans

Huanzhen Ni,†,‡ Weijun Yao,‡ Abdul Waheed,§ Nisar Ullah,*,§ and Yixin Lu*,†,‡
†Graduate School for Integrative Sciences & Engineering (NGS), Centre for Life Sciences (CeLS), National University of Singapore, #05-01, 28 Medical Drive, Singapore 117456 Singapore
‡Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543 Singapore
§Chemistry Department, King Fahd University of Petroleum and Materials, Dhahran 31261, Saudi Arabia

Abstract

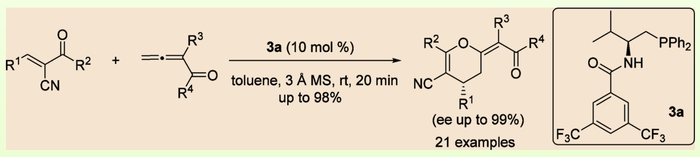


Figure 1. Representative Procedure

An enantioselective [4 + 2]-annulation process between cyano-activated oxadienes and allenones is developed. An L-valine-derived phosphine was efficient in catalyzing the reaction, and a wide range of highly functionalized dihydropyrans were prepared in high yields and with excellent enantioselectivities.

Introduction

- Asymmetric nucleophilic phosphine catalysis has received much attention in the past decade due to its versatility in constructing synthetically useful molecular architectures.
- Phosphine activations of electron deficient allenes and oxadienes, possessing highly activated C–C double bonds leading to a wide range of annulation processes, i.e. [3 + 2]-,2 [4 + 2]-,3 and [4 +1].

The brief History and Literature

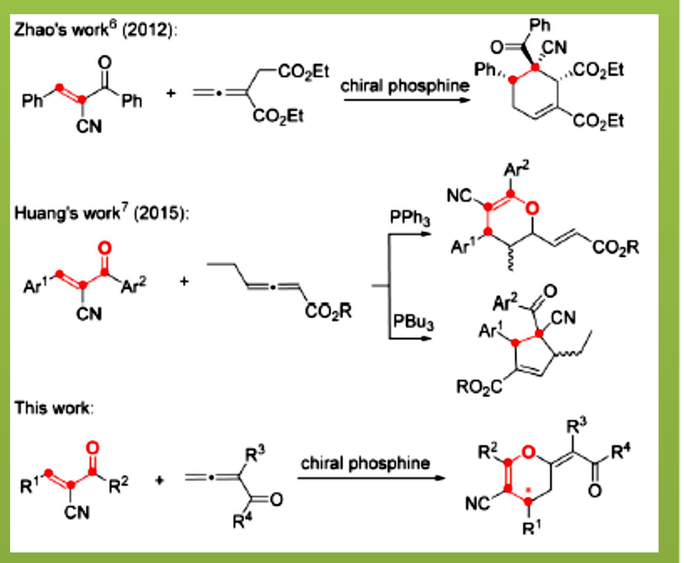


Figure 2. Phosphine Catalyzed Annulation Reactions Employing Oxadienes

The catalyst

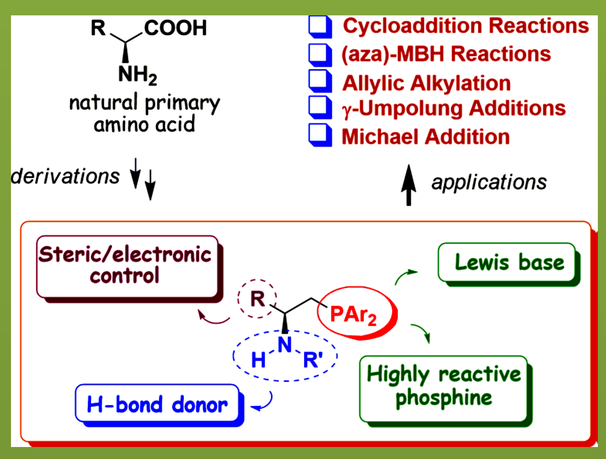


Figure 3. Key backbone for catalyst development

Methods and Materials

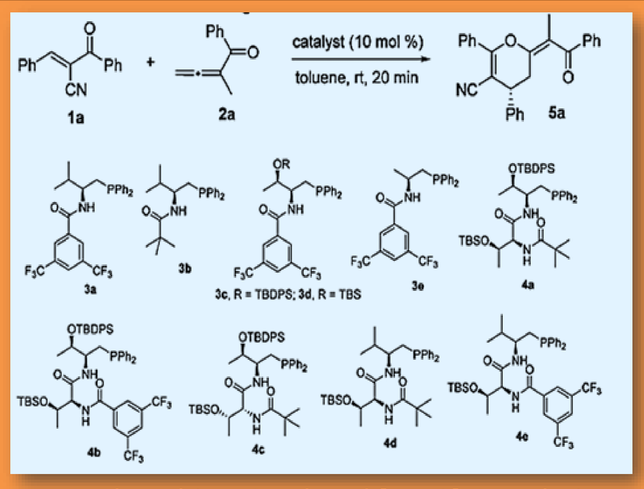


Figure 4. Phosphine-Catalyzed [4 + 2]-Annulation between Oxadiene 1a and Allenone 2a: Initial Screening

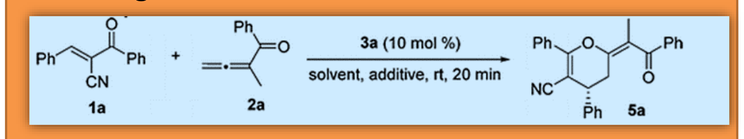


Figure 5. Optimization of the Reaction Conditions

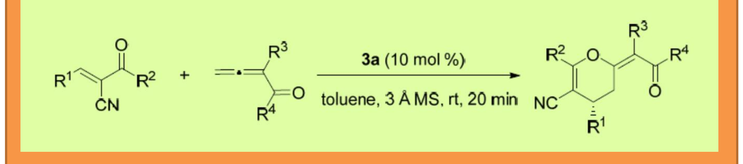


Figure `6. Enhancing the enantioselectivities

Results

Table 1. Phosphine-Catalyzed [4 + 2]-Annulation between Oxadiene 1a and Allenone 2a: Initial Screening

Reactions were performed with 1a (0.1 mmol), 2a (0.12 mmol), and the catalyst (0.01 mmol) in toluene (0.5 mL) at room temperature.
[b]Isolated yield.
[c]Determined by HPLC analysis on a chiral stationary phase.

entry	catalyst	yield (%)[b]	ee (%)[c]
1	$MePPh_2$	80	–
2	**3a**	94	87
3	**3b**	85	84
4	**3c**	87	81
5	**3d**	84	54
6	**3e**	90	75
7	**4a**	86	–80
8	**4b**	89	–73
9	**4c**	70	36
10	**4d**	85	–47
11	**4e**	88	–82

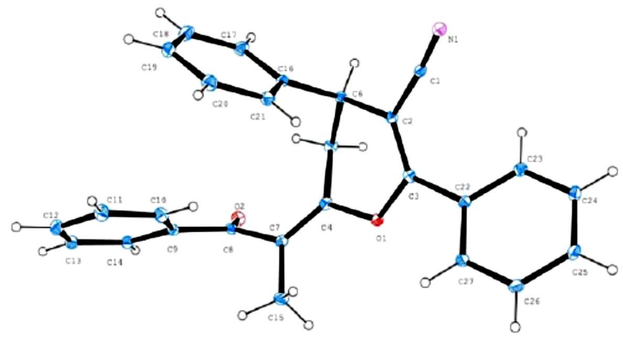
Table 2. Optimization of the Reaction Conditions

Reactions were performed with 1a (0.1 mmol), 2a (0.12 mmol), and 3a (0.01 mmol) under the specified conditions.
[b]Isolated yield.
[c]Determined by HPLC analysis on a chiral stationary phase.

entry	solvent	additive	yield (%)[b]	ee (%)[c]
1	toluene	–	94	87
2	ether	–	90	87
3	ethyl acetate	–	78	75
4	chloroform	–	85	83
5	dichloromethane	–	80	86
6[d]	toluene	–	80	87
7	**toluene**	**3 Å MS**	**95**	**90**
8	toluene	4 Å MS	94	89
9	toluene	5 Å MS	94	90
10[e]	toluene	3 Å MS	90	90
11[f]	toluene	3 Å MS	85	89

Table 3.Scope of the [4 + 2]-Annulation between Oxadiene 1 with Allenone 2a

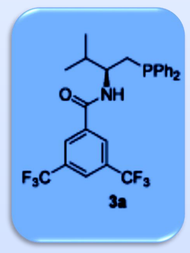
entry	1, R^1/R^2	5	yield (%)[b]	ee (%)[c]
1	**1a**, Ph/Ph	**5a**	95	90
2	**1b**, 4-FC_6H_4/Ph	**5b**	91	92
3	**1c**, 4-ClC_6H_4/Ph	**5c**	94	92
4	**1d**, 4-MeC_6H_4/Ph	**5d**	91	86
5	**1e**, 3-MeC_6H_4/Ph	**5e**	90	85
6	**1f**, 2-MeC_6H_4/Ph	**5f**	94	92
7	**1g**, 4-$MeOC_6H_4$/Ph	**5g**	92	91
8	**1h**, 4-CNC_6H_4/Ph	**5h**	96	91
9	**1i**, 3-$NO_2C_6H_4$/Ph	**5i**	96	94
10	**1j**, 2-naphthyl/Ph	**5j**	94	91
11	**1k**, 2-thienyl/Ph	**5k**	90	90
12	**1l**, (*E*)-PhCH=CH/Ph	**5l**	93	84
13	**1m**, 3-NO_2, 4-ClC_6H_3/Ph	**5m**	94	95
14[d]	**1n**, C_6H_{11}/Ph	**5n**	85	87
15[d]	**1o**, *i*-Pr/Ph	**5o**	79	90
16	**1p**, Ph/*t*-Bu	**5p**	96	90
17	**1q**, Ph/2-thienyl	**5q**	98	93
18	**1r**, Ph/4-ClC_6H_4	**5r**	94	90
19	**1s**, Ph/4-$MeOC_6H_4$	**5s**	95	90



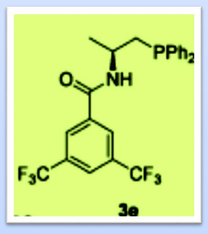
X-Ray Crystallographic Analysis of 5a

Discussion

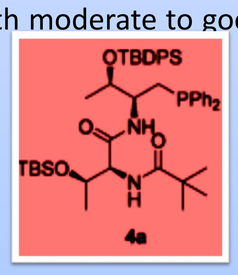
- Simple L-valine-derived amide–phosphine catalysts were very effective.



- Changing the catalyst backbone to threonine or alanine



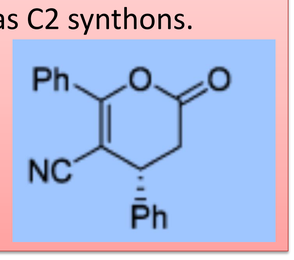
- The L-thr-L-thr-derived catalysts 4a and 4b provided sufficient activation for the reaction and yielded the products with moderate to good ee values.



- (L,L)-dipeptide catalysts led to the formation of products with configurations opposite to those obtained by employing natural amino acid based phosphines.

Conclusions

- The first phosphine catalyzed enantioselective [4 + 2]-cycloaddition between oxadienes and allenones has been develped.
- A unique annulation process with oxadienes as C4 synthons and allenones as C2 synthons.



Contact

Abdul Waheed
King Fahd University of Petroleum and Minerals
Email: g201409980@kfupm.edu.sa
Website: Kkfupm.edu.sa
Phone:0537811650

References

1. Lu, X.;Zhang, C.; Xu, Z. Acc. Chem. Res. 2001, 34, 535.
2. Zhang, C.; Lu, X. J. Org. Chem. 1995, 60, 2906.
3. Wilson, J. E.; Fu, G. C. Angew. Chem., Int. Ed. 2006, 45, 1426.
4. Zhu, X.–F.; Lan, J.; Kwon, O. J. Am. Chem. Soc. 2003, 125, 4716
5. Zhang, Q.; Yang, L.; Tong, X. J. Am. Chem. Soc. 2010, 132, 2550.