Construction of All-Carbon Quaternary Chiral Centers via Michael-Initiated Ring Closure Reaction

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Introduction

All-carbon quaternary stereocenters

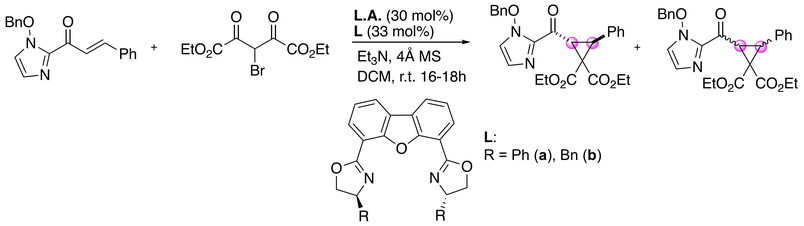
- All-carbon quaternary stereocenters are carbon centers that consist of four carbon substituents.
- They are widely present in many natural products, bioactive molecules and drugs.
- Developing a catalytic method to construct all-carbon quaternary stereocenters in enantioselective fashion is a challenging goal:
  - due to strong steric repulsion between the carbon substituents.
- Installing all-carbon quaternary chiral centers enantioselectively in acyclic system is especially difficult due to conformational flexibility.

Enantioselectivity and cyclopropanation

- Enantioselectivity is a preference for the formation of one enantiomer over the other in a chemical reaction.
- Cyclopropane moieties are widely found in therapeutic agents and biologically active molecules.
- Because most drugs and natural products that contains the cyclopropane ring skeleton are chiral, it is important to develop catalytic methods that produce highly enantioenriched cyclopropanes.
- Michael-Initiated Ring closure (MIRC) reaction with chiral Lewis acid catalysts enables the asymmetric formation of cyclopropanes that contain quaternary and tertiary chiral centers.

Previous Studies

Chiral Lewis acid catalyzed Michael-Initiated Ring Closure (MIRC) reaction to synthesize contiguous tertiary chiral centers



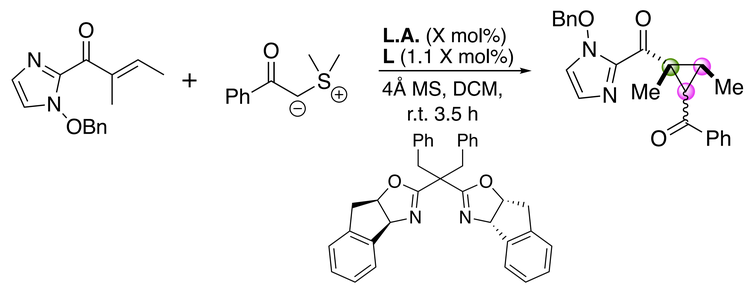
Entry	Lewis acid (L.A.)	Ligand (L)	Time (h)	Diastereomeric ratio (d.r.)	Yield(%)	Enantiomeric excess (ee%)
1	$Co(ClO_4)_2$	**a**	16	99:01	95	26
2	$Ni(ClO_4)_2$	**a**	16	99:01	95	97
3	$Ni(ClO_4)_2$	**b**	16	99:01	80	13
4	$Ni(OTf)_2$	**a**	18	99:01	95	98
5	$Ni(BF_4)_2$	**a**	18	99:01	95	98

Ramkumar Moorthy, Novel asymmetric approaches for the construction of small molecules by cyclization and cycloaddition, **2015**, NDSU

- Addition of α-bromomalonate to α,β-unsaturated carbonyls using chiral Lewis acid catalysts led to substituted cyclopropanes.
- Excellent yields, diastereomeric ratios and enantiomeric excesses were obtained
- Monosubstituted enones were used to access two contiguous tertiary chiral centers.
- After successfully installing tertiary chiral centers, the aim is to make quaternary chiral centers

Results

Chiral Lewis acid catalyzed Michael-Initiated Ring Closure (MIRC) reaction to synthesize all-carbon quaternary and tertiary chiral centers



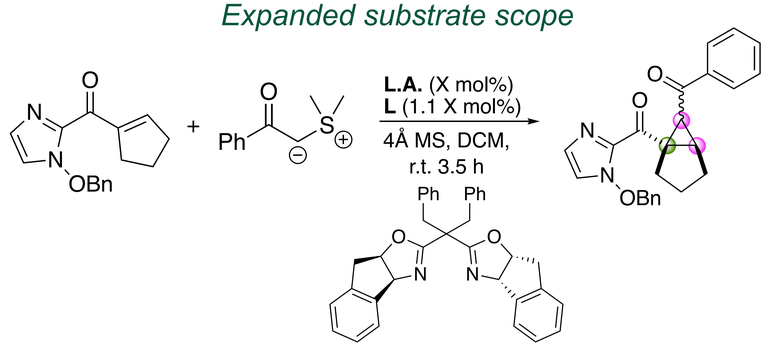
Entry	Lewis acid (L.A.)	Diastereomeric ratio (d.r.)[a]	Yield(%)	Enantiomeric excess (ee%)[b]
1	$Mg(OTf)_2$ (30 mol%)	N.D.	N.R.	N.D.
2	$Mg(NTf_2)_2$ (30 mol%)	N.D.	N.R.	N.D.
3	$Mg(ClO_4)_2$ anh. (30 mol%)	N.D.	N.R.	N.D.
4	$Cu(OTf)_2$ (30 mol%)	N.D.	N.R.	N.D.
5	$Ni(BF_4)_2 \cdot 6H_2O$ (30 mol%)	80:8:12	54	85
6	$Ni(ClO_4)_2 \cdot 6H_2O$ (30 mol%)	77:11:12	81	82
7	$NiBr_2$ (30 mol%)	67:5:28	75	88
8	$NiBr_2$ (20 mol%)	63:6:31	60	81
9	$NiBr_2$ (10 mol%)	76:3:21	72	91
10	$Ni(BF_4)_2 \cdot 6H_2O$ (10 mol%)	83:6:11	73	93

[a] Determined by ^1H NMR
[b] Determined by HPLC. %ee of the major diastereomer. %ee for minor diastereomers are still being investigated.

N.D. Not Determined
N.R. No Reaction

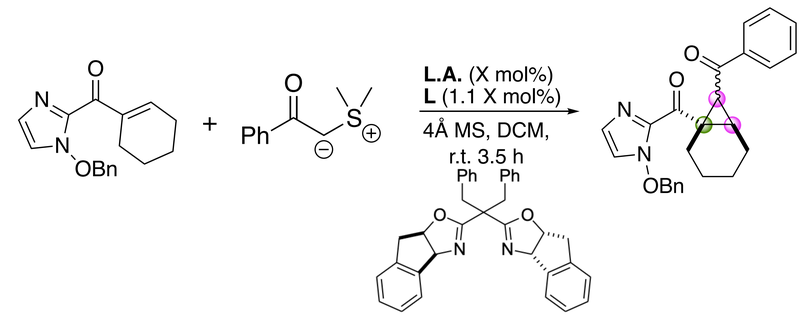
- Addition of sulfur ylide to α,β-unsaturated carbonyls using chiral Lewis acid catalysts led to substituted cyclopropanes featuring contiguous quaternary-tertiary chiral centers.
- Nickel (II) salts including $Ni(BF_4)_2 \cdot 6H_2O$ and $NiBr_2$ with chiral indane-derived bisoxazoline ligand result in excellent enantiomeric excesses as high as 93% ee with good yields.
- Lower catalyst loading leads to better diastereo-, enantioselective products.

Expanded substrate scope



Lewis acid (L.A.)	Diastereomeric ratio (d.r.)	Yield(%)	Enantiomeric excess (ee%)
$Ni(BF_4)_2 \cdot 6H_2O$ (10 mol%)	79:21	91	86 (58)*

*%ee for minor isomer in parenthesis



Lewis acid (L.A.)	Diastereomeric ratio (d.r.)	Yield (%)	Enantiomeric excess (ee%)
$Ni(BF_4)_2 \cdot 6H_2O$ (10 mol%)	79:21	57	91(43)*

*%ee for minor isomer in parenthesis

- Substrates with cyclic system, 5-membered and 6-membered ring, were examined with the developed optimal catalytic condition
- Both substrates produced good diastereo-, enantioselective products with appreciable yields.

Summary and Future Work

- Enantioselective catalytic method that access cyclopropyl rings containing hindered all-carbon quaternary chiral centers via Michael-Initiated Ring Closure reaction was successfully developed.
- Expanding the substrate scope to various scaffolds including α,β-unsaturated carbonyls, N-heterocycles, and amides is currently in progress.

Acknowledgements

The authors thank the Department of Chemistry and Biochemistry at NDSU for the generous financial support.