



Communication

Nickel(II)-catalyzed asymmetric alkylation of acyclic oxocarbenium ions with carboxylic acid derivatives



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ABSTRACT

A nickel(II)-catalyzed asymmetric alkylation of acyclic oxocarbenium ions generated *in situ* from corresponding acetals with carboxylic acid derivatives to prepare β -alkoxyl carbonyl moieties with diverse α -substituents has been disclosed. The method exhibited broad scope of acetals and carboxylic acid derivatives with excellent enantioselectivity and good functional group compatibility, and can be conducted in a gram-scale without obvious loss of efficiency.

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Oxocarbenium ions are key intermediates in a variety of synthetic transformations and in the chemistry of carbohydrates in particular [1]. Catalytic asymmetric addition of carbon nucleophiles to prochiral oxocarbenium ions has remained challenging because they typically lack a Lewis basic site for interaction with chiral catalyst [2]. During the past decade, significant advances have been achieved in enantioselective intermolecular additions to cyclic oxocarbenium ions [3]. In sharp contrast, catalytic asymmetric intermolecular addition to acyclic species has remained undeveloped, presumably due to the lack of rigid geometry [4]. In 2008, Sodeoka disclosed a Pd(II)-catalyzed asymmetric addition of β -ketoesters to acyclic, alkenyl-stabilized oxocarbenium ions generated *in situ* via collapse of acetals [4a]. In 2011, Kobayashi reported a chiral Nb-catalyzed enantioselective addition of silyl enol ethers to acyclic oxocarbenium ions [4b]. The groups of Lambert and Jacobsen respectively documented delicate organo-catalyzed asymmetric alkylation of acyclic, aryl-stabilized oxocarbenium ions with corresponding silyl enol ethers [4c,4d]. Despite great innovation and high enantiocontrol, the specific structures of above mentioned nucleophiles (silyl enol ethers and β -ketoesters) restrict the integrated pattern of functionalities in the α -position of ether derivatives.

Enantiopure β -alkoxyl carbonyl moieties with diverse α -substituents are common building blocks in a number of natural products. *N*-Acetyl thiazolidinethiones derived from diverse

carboxylic acids have been widely used as versatile nucleophiles for aldol reactions of aldehydes to prepare such building blocks through a two-step protocol in complex molecule synthesis [5].

Moreover, since the pioneering work of Urpí, a one-step asymmetric aldol-type addition of chiral *N*-acetyl thiazolidinethiones onto acetals for direct access to chiral β -alkoxyl carbonyls with diverse α -alkyl moieties has been explored [6]. However, catalytic asymmetric variants have been less investigated [7]. Therefore, the development of a catalytic asymmetric alkylation of acyclic oxocarbenium ions generated *in situ* from acetal precursors with diverse carboxylic acid derivatives would enrich the chemistry of oxocarbenium ions and provide an economic and effective method to prepare enantiopure β -alkoxyl carbonyls with diverse α -substituents.

The asymmetric alkylation of benzaldehyde dimethyl acetal **1a** with *N*-(phenylacetyl)oxazolidine-2-thione **2a** was initially selected as a model reaction for optimization using bisoxazoline **L1** (Fig. 1) as chiral ligand, $\text{BF}_3 \cdot \text{OEt}_2$ as acidic additive, and 2,6-lutidine as basic additive in CH_2Cl_2 (Table 1). A variety of metal salt catalysts were evaluated, and $\text{Ni}(\text{OTf})_2$ was identified to be optimal (Table 1, entries 1–4). A further screen of chiral ligands suggested that BINAP **L3** (Fig. 1) furnished the best yields and stereoselectivities (entries 3 and 5–8). Other nickel(II) catalysts such as $\text{Ni}(\text{OAc})_2$ and NiBr_2 together with copper(II) catalysts such as $\text{Cu}(\text{OTf})_2$ afforded inferior results to $\text{Ni}(\text{OTf})_2$ (entries 6 and 9–11). The combination of $\text{BF}_3 \cdot \text{OEt}_2/2,6$ -lutidine proved to be crucial to both the reactivity and *ee*, and replacing either component with TMSOTf or Et_3N was sterile (entries 12–14). The alkylation using pre-prepared **L3**/ $\text{Ni}(\text{OTf})_2$ complex provided a significant improvement in reaction

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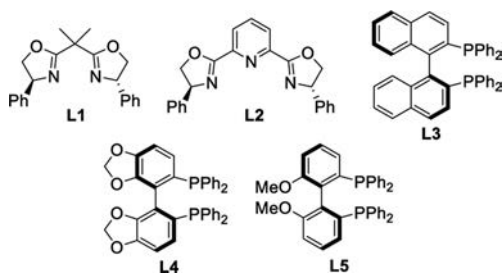


Fig. 1. The chiral ligands.

Table 1

Reaction condition optimization.^a

Entry	L/M	base	Yield (%) ^b	d.r. ^c	ee (%) ^d
1	L1/Mg(OTf) ₂	2,6-lutidine	27	1.2:1	17/18
2	L1/Fe(OTf) ₂	2,6-lutidine	21	1.0:1	9/10
3	L1/Ni(OTf) ₂	2,6-lutidine	42	1.3:1	35/36
4	L1/Cu(OTf) ₂	2,6-lutidine	< 5	n.d.	n.d.
5	L2/Ni(OTf) ₂	2,6-lutidine	< 5	n.d.	n.d.
6	L3/Ni(OTf) ₂	2,6-lutidine	58	1.6:1	95/95
7	L4/Ni(OTf) ₂	2,6-lutidine	47	1.2:1	90/91
8	L5/Ni(OTf) ₂	2,6-lutidine	51	1.4:1	83/84
9	L3/Ni(OAc) ₂	2,6-lutidine	< 5	n.d.	n.d.
10	L3/NiBr ₂	2,6-lutidine	< 5	n.d.	n.d.
11	L3/Cu(OTf) ₂	2,6-lutidine	< 5	n.d.	n.d.
12 ^e	L3/Ni(OTf) ₂	2,6-lutidine	< 5	n.d.	n.d.
13	L3/Ni(OTf) ₂	Et ₃ N	< 5	n.d.	n.d.
14	L3/Ni(OTf) ₂	2,4,6-collidine	51	1.6:1	95/95
15 ^f	L3/Ni(OTf) ₂	2,6-lutidine	80	1.7:1	95/95
16 ^{f,g}	L3/Ni(OTf) ₂	2,6-lutidine	64	1.6:1	95/95
17 ^{f,h}	L3/Ni(OTf) ₂	2,6-lutidine	83	1.6:1	95/95
18 ^{f,i}	L3/Ni(OTf) ₂	2,6-lutidine	86	1.6:1	96/96
19 ^{f,j}	L3/Ni(OTf) ₂	2,6-lutidine	83	1.8:1	98/97

n.d. = not determined.

^a General conditions: To a mixture of **1a** (0.6 mmol, 3.0 equiv.), **2a** (0.2 mmol, 1.0 equiv.), **L** (0.024 mmol, 12 mol%), and metal salt (0.02 mmol, 10 mol%) in CH₂Cl₂ (2.0 mL) at -78 °C was added base (0.6 mmol, 3.0 equiv.) and BF₃·OEt₂ (0.6 mmol, 3.0 equiv.), and the reaction was stirred at r.t. for 3 h, unless otherwise specified.

^b Yield of isolated product.

^c Determined by ¹H NMR spectroscopy.

^d Determined by chiral HPLC analysis.

^e TMSOTf (3.0 equiv.) used instead of BF₃·OEt₂.

^f Pre-prepared L3/Ni(OTf)₂ complex used.

^g BF₃·OEt₂ (2.0 equiv.) and 2,6-lutidine (1.5 equiv.) used.

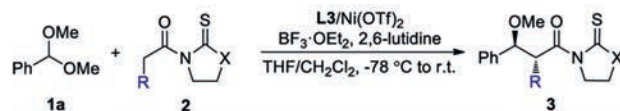
^h BF₃·OEt₂ (2.5 equiv.) and 2,6-lutidine (2.0 equiv.) used.

ⁱ BF₃·OEt₂ (4.0 equiv.) and 2,6-lutidine (3.0 equiv.) used.

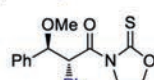
^j CH₂Cl₂/THF (v:v = 1:3) as solvent.

yield (entries 6 and 15). The ratio of BF₃·OEt₂/2,6-lutidine was also found to be very important, and the best results were observed for reaction with excess of acidic additive (entries 15–18). Solvent optimization identified a mixed solvents of CH₂Cl₂/THF (v:v = 1:3) to be optimal, and the expected **3a/3a'** were isolated in 83% yield and 98% ee/97% ee as a separable mixture of diastereomers (d.r. = 1.8:1) (entry 19).

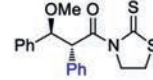
With the optimized reaction conditions in hand, the scope of carboxylic acid derivatives was investigated (Scheme 1). While *N*-(phenylacetyl)-2-oxazolidinone **2c** proved to be an invalid nucleophilic component, *N*-(phenylacetyl)oxazolidinone-thione **2a** and *N*-(phenylacetyl)-thiazolidine-thione **2b** were well compatible



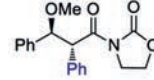
A) R = aryl



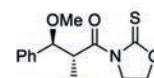
3a, 83%, d.r. = 1.8:1
98% ee / 97% ee



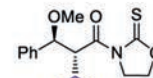
3b, 75%, d.r. = 1.6:1
96% ee / 95% ee



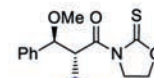
3c, < 5%



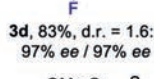
3d, 83%, d.r. = 1.6:1
97% ee / 97% ee



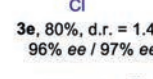
3e, 80%, d.r. = 1.4:1
96% ee / 97% ee



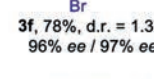
3f, 78%, d.r. = 1.3:1
96% ee / 97% ee



3g, 81%, d.r. = 1.2:1
95% ee / 95% ee

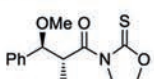


3h, 77%, d.r. = 1.5:1
96% ee / 96% ee

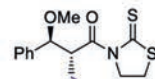


3i, 75%, d.r. = 1.5:1
97% ee / 97% ee

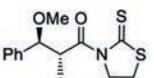
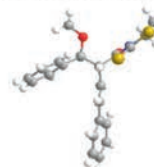
B) R = alkenyl



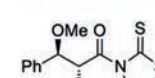
3j, 76%, d.r. = 1.6:1
91% ee / 92% ee



3k, 78%, d.r. = 1.9:1
94% ee / 94% ee

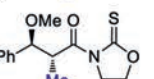


3l, 68%, d.r. = 1.6:1
92% ee / 92% ee

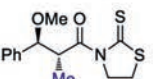


3m, 62%, d.r. = 1.8:1
93% ee / 90% ee

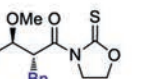
C) R = alkyl



3n, 60%, d.r. = 1.4:1
96% ee / 98% ee



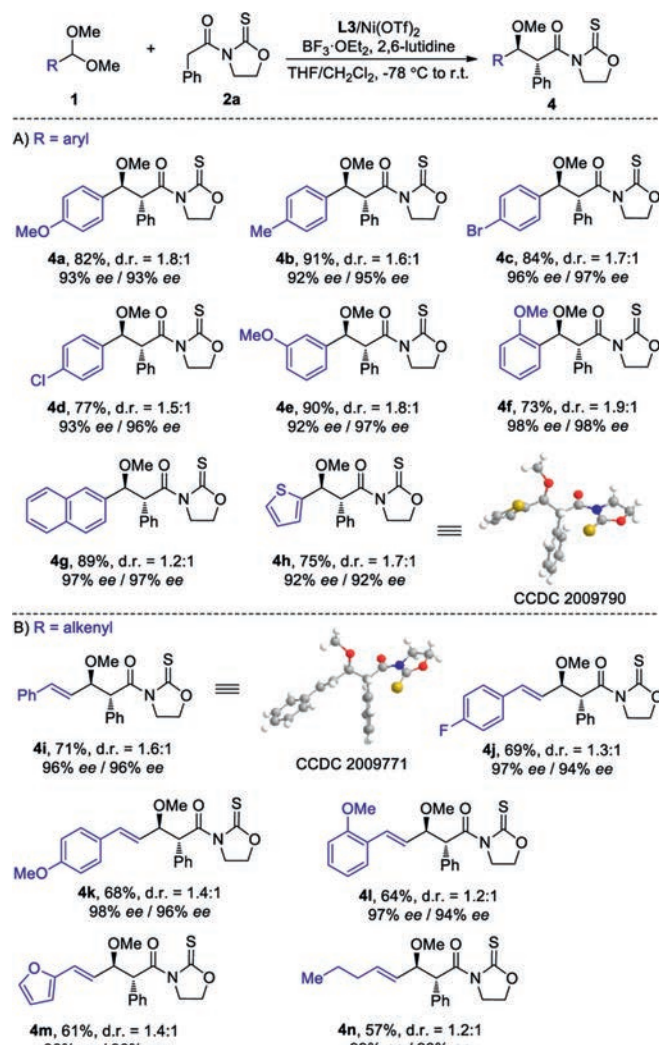
3o, 55%, d.r. = 1.3:1
92% ee / 91% ee



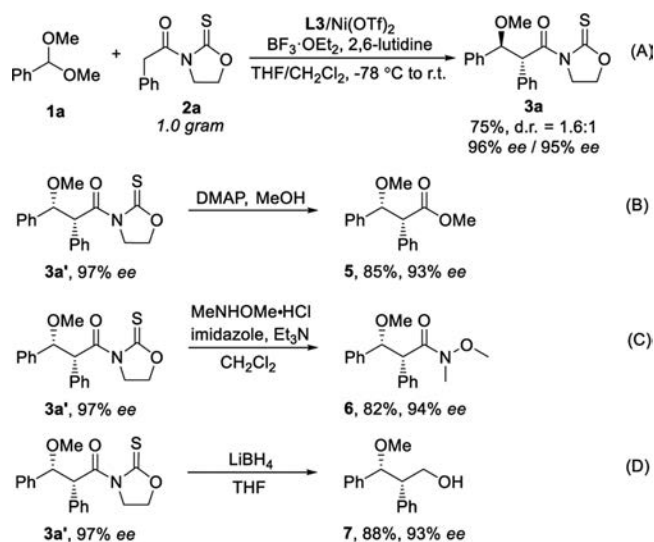
3p, 58%, d.r. = 1.6:1
88% ee / 98% ee

Scheme 1. The scope of carboxylic acid derivatives. d.r. was calculated by separating and weighing two diastereomers.

with the alkylation conditions, with the former to be optimal in terms of efficiency and stereoselectivities (Scheme 1A). A broad range of *N*-(acetyl)oxazolidinone-thiones **2d–2i** bearing electronically varied aryl groups with diverse substituent patterns were tolerated, furnishing corresponding **3d–3i** in good yields (75%–83%) with excellent ee (95%–97%) and moderate diastereoselectivity. α -Alkenyl-substituted acetic acid derivatives were suitable coupling partners (Scheme 1B). γ -Aryl substituted 3-butenoyl **2j** and **2k** together with γ -alkyl substituted **2l** and **2m** were competent substrates, and respective **3j–3m** were obtained in good yields with 91%–94% ee. Notably, all the reactions showed excellent regioselectivity, and the alkylation occurred exclusively at the α -position of 3-butenoyl derivatives with olefin geometry highly conserved. *N*-(Alkylacetyl)oxazolidinone-thiones **2n** and **2p** together with



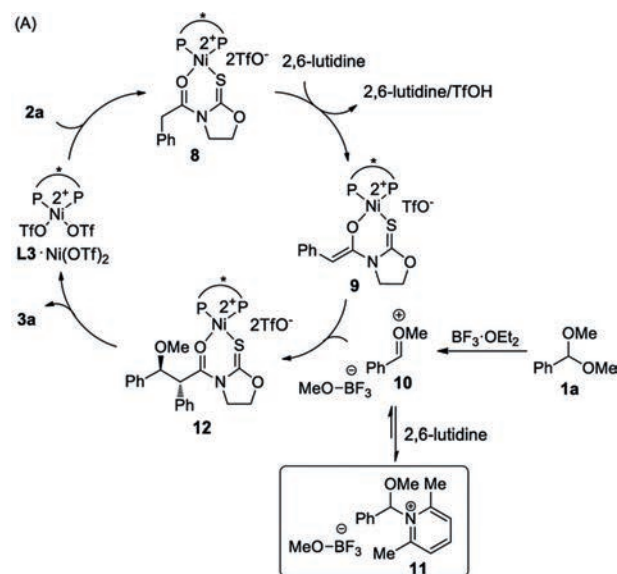
Scheme 2. The scope of acetal components. d.r. was calculated by separating and weighing two diastereomers.



Scheme 3. Synthetic utilities.

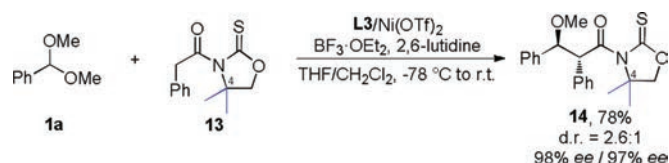
N-(alkylacetyl)-thiazolidine-thione **2o** were also well tolerated (Scheme 1C).

The scope of acetal moieties was then explored (Scheme 2). A variety of aryl-aldehyde dimethyl acetals **1** bearing electronically



(B)

Scheme 4. Proposed reaction mechanism and stereochemistry analysis.



Scheme 5. Substituent effect on 1,3-oxazolidine-2-thione.

varied aryl groups with diverse substituent patterns were well tolerated, furnishing corresponding **4a–4g** in good yields (73–91%) with excellent *ee* (92–98%) and moderate diastereocontrol (Scheme 2A). Heteroaryl aldehyde derived acetal was also suitable substrate, as demonstrated by the generation of **4h** in 75% yield with 92% *ee*. Dimethyl acetals derived from β -aryl and -alkyl substituted acrylaldehydes were also competent substrates, as illustrated by the isolation of **4i–4n** in high efficiency with excellent *ee* (Scheme 2B).

A gram-scale asymmetric alkylation of acetal **1a** with **2a** was conducted without obvious loss of *ee* as well as efficiency, as illustrated by the generation of **3a** in 75% yield with 96% *ee*/95% *ee* (d.r. = 1.6:1) (Scheme 3A). The oxazolidinethione **3a'** can be readily transformed to synthetically valuable methyl ester **5** and Weinreb amide **6**, respectively (Schemes 3B and C). Oxazolidinethione can also be reduced by LiBH₄ furnishing primary alcohol **7** (Scheme 3D).

The mechanism for nickel(II)-catalyzed asymmetric alkylation of benzaldehyde dimethyl acetal **1a** with *N*-(phenylacetyl)oxazolidine-2-thione **2a** was proposed (Scheme 4A). **2a** coordinates with prepared L3/Ni(OTf)₂ catalyst giving **8**. In complex **8**, the hydrogen α to the carbonyl moiety was activated in terms of the acidity. 2,6-Lutidine facilitates the enolization of **8** furnishing chiral Ni-bound *Z*-enolate **9** [8]. **9** attacks acyclic oxocarbenium **10** generated *in situ* from **1a** and BF₃·OEt₂ providing **12**. Product dissociation completes the catalytic cycle. No reactivity was observed when Et₃N was used

instead of 2,6-lutidine or 2,4,6-collidine, suggesting that the role of pyridine derivatives might not simply act as a base (entries 6, 13 and 14, Table 1) [9]. It has been known that acetal might react with 2,4,6-collidine affording corresponding pyridinium-type salt [10,7b]. Accordingly, we envisioned that 2,6-lutidine might react with acyclic oxocarbenium **10** reversibly giving pyridinium **11**. **11** possessing weak electrophilicity might be regarded as a reservoir of **10** to prevent the decomposition before the attack by enolate **9**. The stereochemical induction model was proposed in Scheme 4B [7]. The P-bound phenyl group on the ligand (in red) shields the top face (*Re* face) of the enolate substrate (in blue), which disfavors the electrophilic attack by the oxocarbenium intermediate. In contrast, the addition of the oxocarbenium ion to the *Si* face of the enolate substrate is favored because of less repulsive interactions with the ligand. The observed moderate diastereoselectivity might be ascribed to the lack of Lewis basic site on corresponding oxocarbenium ion intermediates for substrate–catalyst interactions.

Based on above analysis, we envisioned that placing a germinal substitution at the C4 of 1,3-oxazolidine-2-thione might be beneficial for improving the d.r.. Under the standard conditions, asymmetric alkylation of acetal **1a** with **13** bearing a germinal dimethyl substitution proceeded, furnishing expected **14** in 78% yield and 98% *ee*/97% *ee* as a separable mixture of diastereomers (d. r. = 2.6:1), indicating that modification of 1,3-oxazolidine-2-thione might be a viable approach for enhancing the diastereoselectivity (Scheme 5).

In conclusion, a nickel(II)-catalyzed asymmetric alkylation of acyclic oxocarbenium ions generated in situ from corresponding acetals with carboxylic acid derivatives to prepare β -alkoxyl carbonyl moieties with diverse α -substituents has been disclosed. The method exhibited broad scope of acetals and carboxylic acid derivatives with excellent enantioselectivity and good functional group compatibility, and can be conducted in a gram-scale without obvious loss of efficiency.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ccl.2020.08.034>.

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