

Cobalt-Stabilized Propargylic Oxocarbenium Ions Enable Direct and Asymmetric Nickel(II) Catalyzed Aldol-Like Reactions

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Cite This: *Org. Lett.* 2026, 28, 9312–9317



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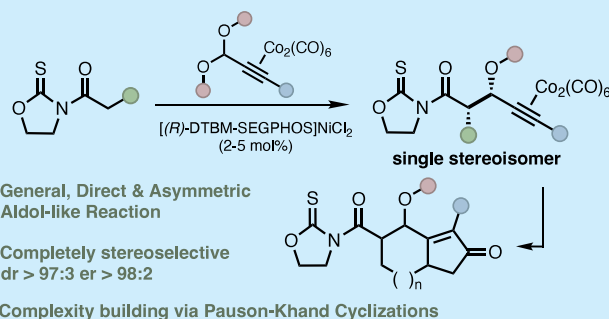


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ABSTRACT: We describe a direct and asymmetric aldol-like reaction between a wide range of *N*-acyl-1,3-oxazolidine-2-thiones and cobalt-protected propargylic acetals catalyzed by a chiral nickel(II) complex leading to *syn* β -alkoxy derivatives. This overcomes longstanding limitations associated with acetals from aliphatic aldehydes, selectively providing *syn* aldol adducts in excellent yields as single stereoisomers (dr >97:3, er up to >99:1). Furthermore, the cobalt fragment enables downstream intra-molecular Pauson-Khand cyclizations, granting rapid access to densely functionalized bicyclic architectures.



Despite the tremendous advances in asymmetric catalysis over recent decades, many reported methods still suffer from narrow substrate scopes and rely on structurally complex chiral catalysts, limiting their synthetic utility.¹ Accordingly, the development of reliable and broad-scope methods for the stereocontrolled synthesis of carbon architectures, capable of meeting the growing demand for more efficient routes to biologically active compounds and novel chiral agrochemicals or materials, has attracted considerable interest.^{2–5}

In this context, metal enolates stand out as privileged intermediates for the asymmetric construction of carbon–carbon bonds catalyzed by chiral metal complexes,^{6,7} with aldol reactions among the most prominent applications.^{8,9} Early approaches in this area relied on the stoichiometric generation of silyl enolates prior to the catalytic reaction, with clearly defined nucleophilic and electrophilic roles.¹⁰ By contrast, the seemingly simpler, and more convenient direct variants, in which a carbonyl adds to another in the presence of a chiral catalyst, remain a significant challenge. Against this background, pioneering studies by Shibasaki,¹¹ Trost,¹² and Evans¹³ demonstrated the feasibility of direct aldol reactions catalyzed by chiral metal complexes and laid the groundwork for further advances.¹⁴

Inspired by these precedents, we launched a few years ago a research project aimed at establishing a common strategy for the stereoselective formation of carbon–carbon bonds based on an S_N1 -like mechanism, an approach that hinges on electrophiles such as activated aldehydes or oxocarbenium ions.¹⁵ This strategy proved effective and the results met our expectations, as we were able to establish enantioselective syntheses of *protected* aldol adducts from thioimides in a single step using easy to handle chiral nickel(II) complexes, a silyl

triflate, and lutidine.^{16,17} Unfortunately, the generation of the nickel(II) enolates was sometimes incompatible with the activation of the necessary electrophiles, such as aliphatic aldehydes or their acetal counterparts, thereby restricting the reacting species to those derived from aromatic systems (Scheme 1a). To overcome this limitation, we envisioned α,β -unsaturated aldehydes as suitable alternatives.¹⁸ However, controlling the preference toward the 1,2- over the 1,4-addition proved challenging, making the regioselectivity, together with the diastereo- and the enantioselectivity, a major hurdle in the overall transformation.^{19,20} We therefore reasoned that cobalt-protected propargylic aldehydes or acetals might be an appealing option because (i) the coordination of the triple bond to cobalt would suppress the 1,4-addition; (ii) the electrophile would be further activated through charge delocalization onto the cobalt complex,^{21,22} and (iii) the resulting complexes would serve as versatile platforms for building molecular complexity (Scheme 1b).

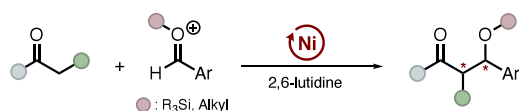
Herein, we report a highly stereocontrolled aldol-like addition of *N*-acyl-1,3-oxazolidine-2-thiones to dicobalt hexacarbonyl dialkyl propargylic acetals catalyzed by a chiral nickel(II) complex to give *protected syn* aldol adducts.²³ Subsequent reduction of the carbon–carbon triple bond provides access to formal aldol products of saturated and

Received: June 3, 2026
Revised: June 23, 2026
Accepted: June 26, 2026
Published: July 3, 2026

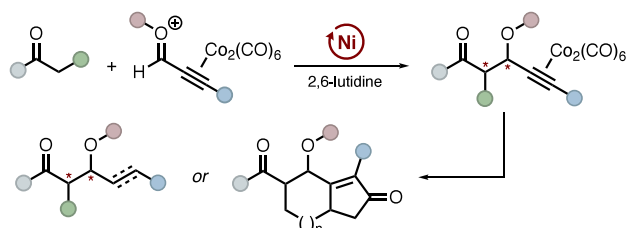


Scheme 1. Direct, Asymmetric, and Catalytic Aldol Reactions

(a) Prior approaches using aromatic oxocarbenium intermediates



(b) Current approach using propargylic oxocarbenium intermediates



α,β -unsaturated acetals. Moreover, leveraging on the presence of the cobalt complex, the protected adducts undergo Pauson-Khand cyclizations to yield enantiomerically pure bicyclic architectures (Scheme 1b).²⁴

With a well-established enolate platform consisting of thioimides and nickel(II) catalysts bearing chiral diphosphine ligands,^{15,25} we began our investigations by evaluating the nature of the electrophile. While the protected phenyl propargyl aldehyde afforded complete regioselectivity toward the desired aldol adduct, it exhibited lower diastereoselectivity and yield compared to the protected analogue from the commercially available diethyl acetal **2a** (entries 1 and 2, Table 1). Consequently, cobalt-complexed propargylic acetals were identified as optimal electrophiles for this transformation. Then, following a comprehensive optimization of the experimental conditions, it was established that the TMSOTf-mediated aldol reaction of *N*-propanoyl-1,3-oxazolidine-2-thione (**1a**) and diethyl acetal **2a**, catalyzed by 2 mol % [(*R*)-DTBM-SEGPHOS]NiCl₂ gave quantitatively the protected *syn* aldol adduct **3a** as a single stereoisomer (dr >97:3 and er >99:1; Table 1).^{25,26} In contrast, the unprotected acetal failed to furnish the desired product (entry 3, Table 1).

Likewise, low conversions were observed in the absence of the nickel catalyst (entry 4, Table 1). In turn, other thioimides, chiral phosphines, silyl triflates or solvents of varying polarity (entries 5–8, Table 1) proved less effective. Finally, the use of two equivalents of TMSOTf was essential to attain full conversion (entry 9, Table 1).

With the optimized reaction conditions and the extremely promising results obtained for acetal **2a** in hand, we examined the direct TMSOTf-mediated aldol-like reaction of a variety of *N*-acyl-1,3-oxazolidine-2-thiones (**1a–g**) with a broad range of cobalt-protected dialkyl acetals (**2a–l**) catalyzed by [(*R*)-DTBM-SEGPHOS]NiCl₂. The results are summarized in Table 2.

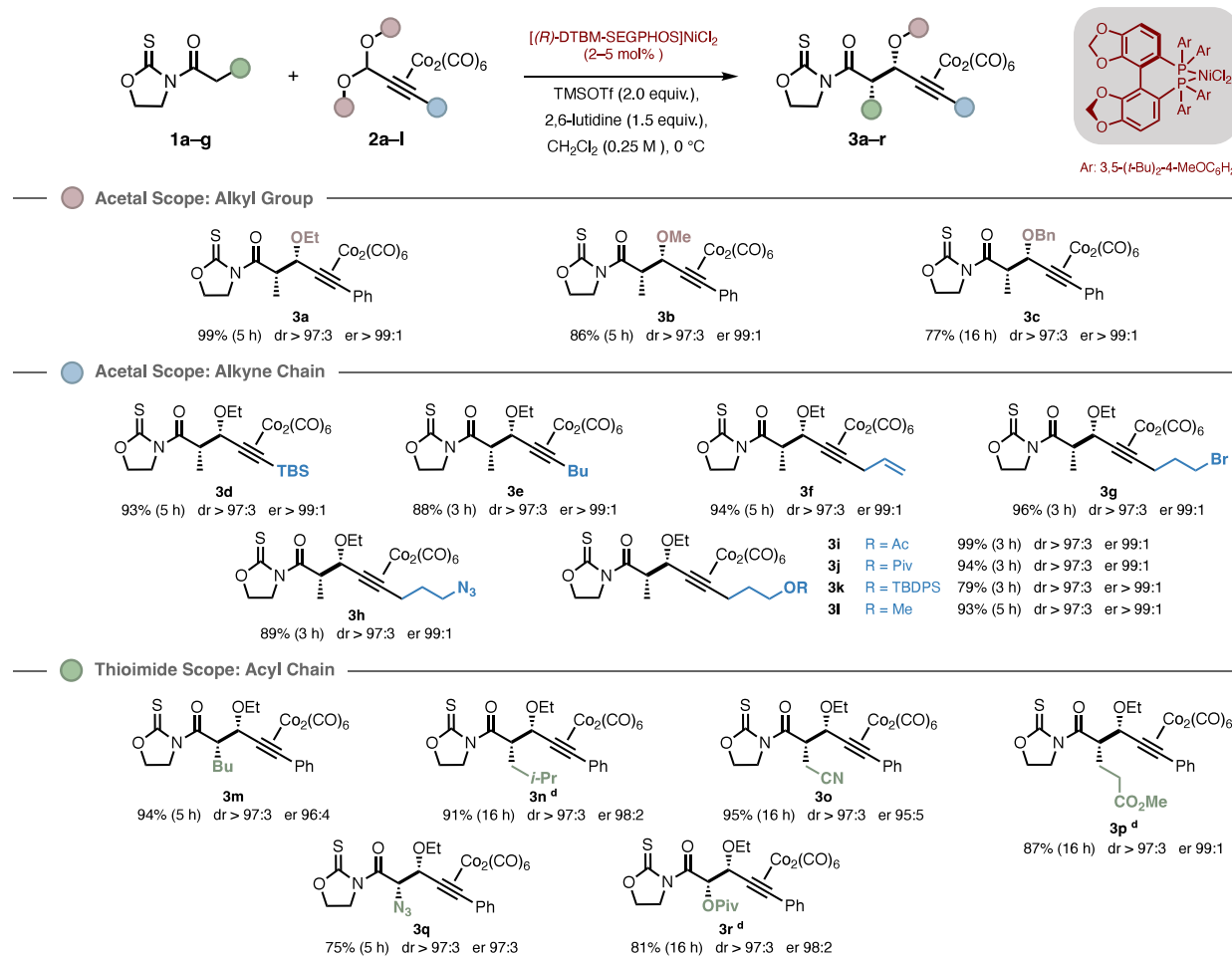
Acetals derived from protected phenylpropargylic aldehyde performed with similar efficiency. Indeed, both dimethyl and dibenzyl acetals, **2b** and **2c** respectively, provided the corresponding adducts **3b** and **3c** in high yields and with complete stereocontrol. Next, we investigated the effect of replacing the phenyl group in the diethyl acetal. While the terminal alkyne proved to be unsuitable, its silylated counterpart **2d** produced the aldol adduct **3d** as a single stereoisomer in high yield. Furthermore, propargylic acetals bearing either a simple alkyl group or more elaborate chains incorporating alkenes, halides, azides, or esters, consistently delivered the desired adducts **3e–j** in outstanding yields and with complete stereocontrol (dr >97:3, er 99:1). In contrast, free alcohols were poorly tolerated, although silyl ether or methyl derivatives **2k** and **2l** afforded the corresponding adducts **3k** and **3l** in stereochemically pure manner in high yields.

The reactivity of more elaborate thioimides **1a–g** bearing different acyl groups was also evaluated (Table 2). Longer and bulkier alkyl substituents, such as **1m** (*n*-Bu) and **1n** (*i*-Bu), were well tolerated, as were more functionalized alkyl chains containing nitrile (**1o**) or ester (**1p**) groups. The optimized conditions were likewise compatible with thioimides bearing heteroatoms at the α position, such as an azide (**1q**) or a protected alcohol (**1r**). Remarkably, all protected aldol adducts **3m–r** were obtained in excellent yields as single stereoisomers, although in some cases an increased catalytic loading of up to 5 mol % was needed to achieve full conversion.

Table 1. Optimization of the Reaction Conditions

Entry	Deviation from standard conditions	3a (%) ^a	dr ^b	er ^c
1	—	99	>97:3	>99:1
2	Aldehyde instead of acetal	26	78:22	nd
3	No Co protection	nr	nr	nr
4	No catalyst	8	>97:3	nd
5	[(<i>S</i>)-Tol-BINAP]NiCl ₂	68	>97:3	97:3
6	Other thioimides	37–76	>97:3	nd
7	Other solvents (DCM/Tol, EtOAc)	78–87	>97:3	nd
8	TESOTf instead of TMSOTf	52	>97:3	nd
9	TMSOTf (1.5–1.8 equiv)	81–91	>97:3	nd

^aIsolated yields. ^bDiastereomeric ratios were determined by ¹H NMR analysis of the crude. ^cEnantiomeric ratios were determined by chiral HPLC analysis.

Table 2. Scope of the Reaction^{a,b,c}

^aAll reactions were performed on 0.25–0.5 mmol scale with 1.0 equiv of thioimides **1a–g** and 1.1 equiv. protected propargylic acetals **2a–l**.

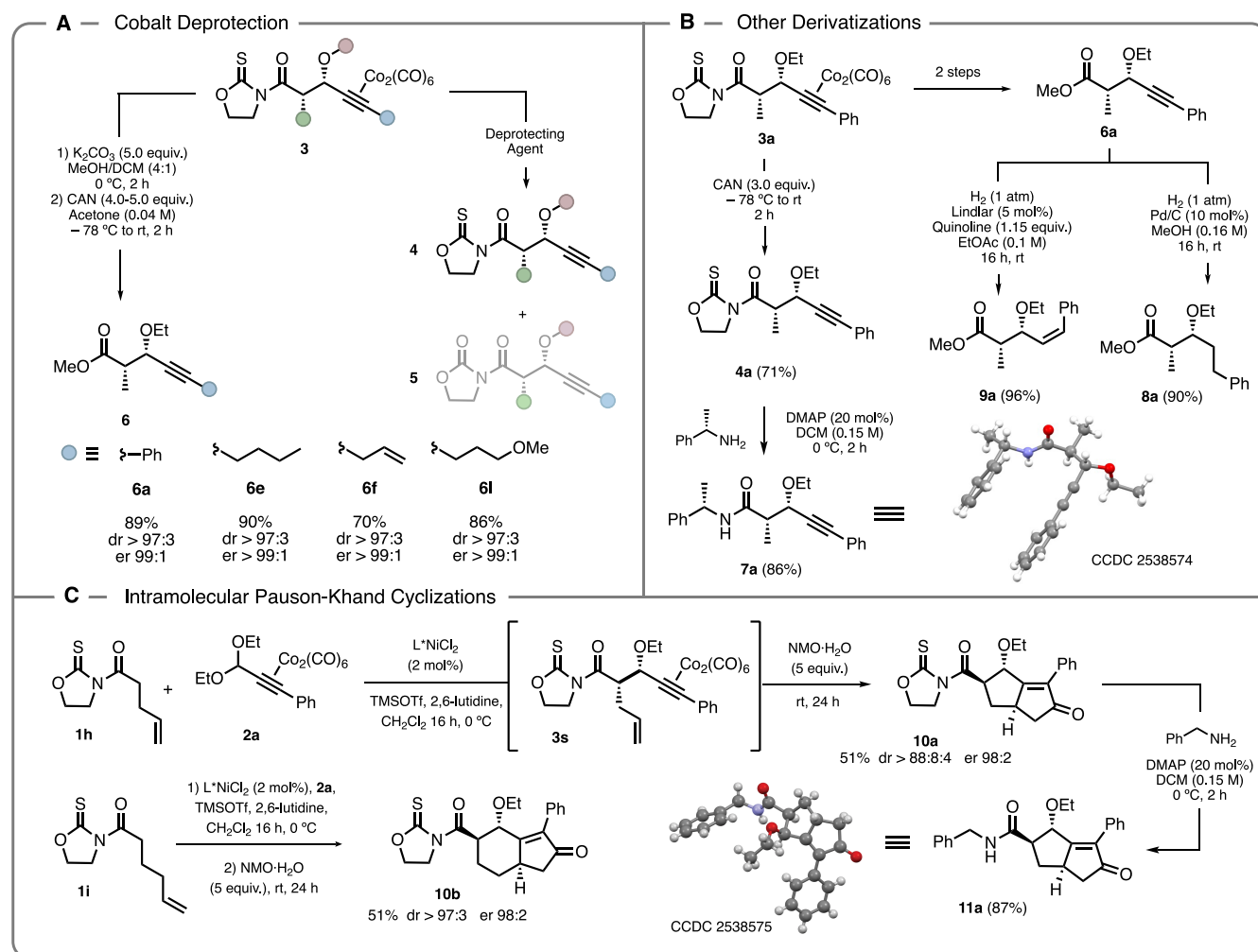
^bDiastereomeric ratios were determined by ¹H NMR (400 MHz) analysis of the crude. ^cEnantiomeric ratios were determined by chiral HPLC analysis. ^dReaction carried out with 5 mol % of the chiral nickel(II) complex.

To demonstrate the synthetic versatility of this new aldol-like reaction, the resultant adducts were subjected to a variety of transformations. We first targeted the decomplexation of the cobalt-protected adduct **3a** using CAN in acetone leading to thiazolidinethione **4a** (Scheme 2A). Under these conditions, a minor byproduct arising from oxidation of the heterocyclic thiocarbonyl bond (**5a** in Scheme 2A) was also detected.²⁷ Alternative reagents, including Fe(NO₃)₃·9H₂O or NMO, led to the formation of the oxazolidinone **5a** too. Eventually, careful reaction monitoring under the initial conditions (CAN in acetone) minimized the formation of the oxazolidinone derivative without altering the stereochemical integrity of either the aldol adducts or the resulting oxazolidinone derivatives.²⁵ Although these conditions proved acceptable, we sought to completely prevent the oxidation pathway. Since the heterocycle is ultimately converted into other carboxylic derivatives, we envisaged that its removal prior to the decomplexation step could circumvent this undesired reaction. As a proof of concept, we designed a simple three-step sequence to synthesize methyl esters **6**, requiring only a single purification and affording the corresponding carboxylic derivatives in high yield with outstanding diastereo- and enantioselectivity (dr > 97:3, er > 99:1) across a range of substrates (Scheme 2A). Adduct **3a** could also be deprotected

and the thioimide platform displaced with (*S*)-methylbenzylamine to afford crystalline amide **7a**. Its absolute configuration was unambiguously established by X-ray analysis, thereby confirming the stereochemical assignment of adduct **3a** (Scheme 2B). Furthermore, the triple bond of ester **6a** was either completely reduced to **8a** or selectively into the (*Z*)-alkene **9a** (Scheme 2B).²⁸ These and the above-mentioned transformations highlight the synthetic potential of this method to access a broad array of enantiomerically pure aldol derivatives.

Having established a direct, asymmetric, and broadly applicable aldol-like reaction, we envisioned that the cobalt complex could serve a dual purpose. Beyond its protective role, it might enable access to structurally intricate polycyclic frameworks through intramolecular Pauson–Khand cyclizations²⁹ of substrates bearing a suitably positioned olefin. Such a demanding transformation would require careful control to ensure compatibility between the olefin and the cobalt-protected alkyne until the cyclization was triggered. Exploratory studies on allyl acetals as precursors to oxygenated heterocycles indicated that the intramolecular cyclization was problematic, likely owing to the tendency of the olefin and the cobalt-protected alkyne to react in previous steps of the synthetic sequence. Therefore, we turned our attention to

Scheme 2. Transformations of the Aldol Adducts



thioimides bearing an olefin within the acyl group. Specifically, we assayed the construction of the tetrahydropentalen-2(1*H*)-one bicyclic core starting from *N*-(4-pentenyl)-1,3-oxazolidine-2-thione (**1h** in Scheme 2C). Under the optimized conditions (Table 1), the reaction of thioimide **1h** and diethyl acetal **2a** gave the expected aldol adduct quantitatively as a single diastereomer; however, it could not be isolated due to partial spontaneous cyclization on silica gel.³⁰ Accordingly, the intramolecular Pauson-Khand cyclization was attempted directly on the crude reaction mixture. A range of conditions was thus screened. Initial trials led to the formation of numerous side products arising from oxidation of the exocyclic C = S bond, cobalt decomplexation, and/or simple degradation of the starting materials. Among the promoters tested, NMO·H₂O emerged as the best candidate.²⁹ Following this choice and after considerable experimentation, suitable conditions were identified under which a main diastereomer was observed in the crude mixture, though careful HPLC-MS analysis revealed two minor species with identical mass and fragmentation patterns in an approximate ratio of 88:8:4 based on chromatographic peak areas. Since no improvement was achieved with solvents other than dichloromethane, the same solvent used in the preceding aldol addition, a one-pot procedure was adopted. This protocol ultimately afforded bicycle **10a** in 51% isolated yield over two steps, with an

enantiomeric ratio of 98:2. The absolute configuration was determined through conversion into crystalline amide **11a** and subsequent X-ray studies (Scheme 2C). Notably, this one-pot procedure seamlessly enabled the formation of four carbon–carbon bonds in a stereocontrolled manner and with good overall yields. The optimized procedure was next applied to thioimide **1i** to access hexahydro-2*H*-inden-2-one analogue **10b** in good yield as a single stereoisomer (Scheme 2C).³¹

The high level of stereochemical control in the carbon–carbon bond forming step prompted mechanistic considerations. Based on the conversion of the nickel chloride complexes into the correspondent triflates described by Sodeoka³² and our prior studies on aldol-like reactions of thioimides and oxocarbenium ions,¹⁵ the catalytic cycle in Scheme 3 is proposed. Both the enolization step leading to chelated enolate **III**, or the formation of the oxocarbenium intermediate **IV** by reaction of TMSOTf with the dialkyl acetal,^{15,33} ultimately provide an enantiomeric ratio of up to 99:1 that likely originates from the chiral ligands of the nickel(II) complex, which dictate the π facial selectivity of the nickel enolate through an open transition state as **V**. In contrast, the absolute diastereocontrol is attributed to the steric bulk of the cobalt-protected acetal moiety, which preferentially orients away from the thioimide scaffold. Accordingly, alkyne protection not only stabilizes the

experimental research and wrote the Supporting Information. C.P. is responsible for the X-ray analyses. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Financial support from the Spanish Ministerio de Ciencia, Innovación y Universidades (MICIU/AEI/10.13039/501100011033/FEDER, UE, Grant PID2024-158213NB-I00), and the Generalitat de Catalunya (2021SGR 268), as well as a doctorate studentship to X. T. (Formación de Profesorado Universitario-FPU22/01103, MICIU) and Erasmus+ Program Grants to L. O., E. B., and E. D. are gratefully acknowledged.

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NOTE ADDED AFTER ASAP PUBLICATION

Scheme 2 was corrected on July 8, 2026.