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Ni-catalyzed cross-electrophile coupling of α -hydroxy carbonyl compound-derived oxalates with vinyl triflates

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Introduction

The β,γ-unsaturated carbonyl compounds containing two proximal chromophores are often-used reagents and continue to be used in synthetic chemistry [1]. Accordingly, their preparation has been intensively explored, and remarkable progress has been attained over the past few decades. The methods include the direct nucleophilic substitution of acyl electrophiles using allylic organometallic reagents [2], and the α -vinylation of nascent enolates employing vinyl nucleophiles by organocatalysis [3,4]. Alternatively, transition metal-catalyzed α -vinylation of enolates with vinyl electrophiles has also emerged as an important strategy (Scheme 1a) [5,6]. Moreover, metal-catalyzed cross-coupling of α -halocarbonyl electrophiles with vinyl nucleophiles or halides provides another effective approach to access β , γ -unsaturated carbonyl compounds (Scheme 1b) [7]. In this regard, nickel has displayed a unique ability to promote such coupling reactions through radical pathways, in particular for the enantioconvergent transformations [8].

On the other hand, the utilization of C–O electrophiles instead of C–X (X = halide) electrophiles within the cross-coupling arena has recently attached considerable attention [9]. This is largely due to the hypotoxicity, ready accessibility and low cost of hydroxyl-containing compounds. For instance, Shu and co-workers reported that primary benzyl oxalates were able to couple with alkyl bromides under reductive conditions [10]. Independently,

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ABSTRACT

A nickel-catalyzed reductive vinylation of α -hydroxy carbonyl compound-derived C–O electrophiles to access β , γ -unsaturated carbonyl compounds is reported here. By this method, a library of vinyl triflates can serve as vinylating reagents, while various alkyl oxalates undergo C–O bond fragmentation to provide α -carbonyl radicals. This work expands the scope of cross-electrophile coupling reactions that employ two low toxic C–O electrophiles as coupling partners.

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the research group of Gong showcased that oxalates derived from tertiary alcohols and α hydroxy esters engaged in the nickel-catalyzed reductive coupling reactions with aryl electrophilies [11,12]. Inspired by these, we thus set out to explore the formation of appealing β , γ -unsaturated carbonyl compounds, starting from two easily accessible C–O electrophiles. Herein, we report a mild nickel-catalyzed cross-electrophile coupling of α -hydroxy ester and ketone-derived oxalates with vinyl triflates via C–O/C–O bond cleavage (Scheme 1c). This protocol features good coupling efficiency and broad substrate scope, and is therefore a useful complementary to the existing methods to afford β , γ -unsaturated carbonyl compounds.

Result and discussion

We began by investigating the cross-coupling of α hydroxy ester-derived oxalate **1a** with cyclic vinyl triflate **2a** to access β , γ -unsaturated ester **3aa** (Table 1). After substantial optimization, high yield was obtained by using NiCl₂(dppe) as catalyst, dtbpy as ligand and Zn as reductant in the presence of MgCl₂ and tetrabutylammonium iodide (TBAI) in dimethylformamide (DMF) (entry 1). Control experiments disclosed that nickel salt, ligand, reductant and MgCl₂ are necessary and TBAI as additive is crucial to secure the high yield (entries 2–5) [13]. Changing different nickel catalysts did not give better results (entries 6–9). It was also found that other bidentate ligands **L2–L4** resulted in lower coupling efficiency (entries 10–12), and tridentate ligand **L5** led to the formation of coupled product in trace amount (entry 13).

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(a) Vinylation of nascent enolates



(b) Vinylation of α -halocarbonyl compounds



(c) Vinylation of activated α -hydroxy carbonyl compounds (this work)



Scheme 1. Metal-catalyzed formation of β , γ -unsaturated carbonyl compounds. TM = transition metal. Tf = trifluoromethanesulfonate.

Of note, the practicality of this method was demonstrated in a large scale reaction, wherein the desired product **3aa** was formed in 72% yield (entry 14).

With the optimized conditions in hand, we then evaluated the scope of vinyl triflates, which can be readily prepared from ubiquitous ketone precursors (Scheme 2).[14,15] In addition to the model substrate **2a**, both nonsubstituted cyclic and heterocyclic vinyl triflates were capable of coupling with **1a**, providing corresponding products **3ab–3af** in moderate to good yields. Cyclohexenyl triflates decorated with a variety of substituents were also effective vinylation reagents, as exemplified by the formation of **3ag–3ai**

Table 1

Optimization of reaction conditions.



Entry	Variation of the standard condition	Yield (%) ^{a,b}
1	None	87(82) ^c
2	w/o NiCl ₂ (dppe)	ND
3	w/o Zn	ND
4	w/o MgCl ₂	trace
5	w/o TBAI	70
6	Ni(cod) ₂ instead of NiCl ₂ (dppe)	50
7	Ni(acac) ₂ instead of NiCl ₂ (dppe)	46
8	NiCl ₂ instead of NiCl ₂ (dppe)	26
9	NiCl ₂ (dppf) instead of NiCl ₂ (dppe)	24
10	L2 instead of L1	72
11	L3instead of L1	72
12	L4 instead of L1	71
13	L5 instead of L1	trace
14	4.0 mmol of 1a	72

ND = not detected; cod = 1,5-cyclooctadiene; acac = acetylacetone.

^a The reaction was performed on a 0.15 mmol scale.

^b Determined by ¹H NMR analysis using 2,5-dimethylfuran as internal standard.

^c Isolated yield after column chromatography.



Scheme 2. Scope of vinyl triflates for the coupling with **1a** and **1b**. ^aDetermined by ¹H NMR analysis using 2,5-dimethylfuran as internal standard. 2-Nap = 2-naphthyl

and **3ak–3am** in high yields. In contrast, phthalimide substituted vinyl triflate converted into **3aj** in rather moderate yield, and the deoxygenative reduction of both electrophiles was observed as side reactions. Likewise, such side reactions were deleterious to the formation of esters **3an** and **3ao**, when conjugated vinyl triflates **2n** and **2o** were utilized. Acyclic vinyl triflates were also tested to couple with **1b** under the standard condition. β , γ -Unsaturated ester **3bp** was formed in 50% yield, whereas more sterically hindered **2q** was less effective, providing **3bq** in 20% yield.

Subsequently, we examined the generality of alkyl oxalates as coupling partners in this protocol (Scheme 3). Notably, 2-hydroxypropanoic acid-derived oxalates containing a wide range of *O*-aryl and alkyl ester moieties, which vary in electronic effect, were all amenable to the standard setup, thus furnishing **3ba**–**3ha** in moderate to high yields. Alkyl groups such as ethyl, butyl and functionalized alkyl chains at the α -position of ester were investigated as well. Coupled products **3ia**–**3la** were produced in lower yields, likely due to the higher steric hindrance compared to that of a methyl group. Similarly, more hindered tertiary alkyl oxalates only afforded **3na** in 10% ¹H NMR yield. The method was also applicable to alkyl oxalates derived from α hydroxy lactone and ketone, wherein **3ma** and **3oh** were delivered in moderate yields, respectively.

Next, we turned to explore the enantioconvergent version of the model reaction by changing the combination of reaction parameters. It was eventually disclosed that **3aa** was isolated in 50% yield and 15% ee by using Ni(cod)₂/**L6** in THF at 0 °C (Eq. (1)).



(1)

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Scheme 3. Scope of alkyl oxalates for the coupling with **2a** and **2h**. ^aDetermined by ¹H NMR analysis using 2,5-dimethylfuran as internal standard.

In line with the previous studies on nickel-catalyzed cross-coupling of alkyl oxalates,[10,11] we believe that the present vinylation reaction also proceeds through the radical mechanism, involving alkyl radical intermediates. Indeed, the addition of radical inhibitor, i.e., (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), to the model reaction resulted in no conversion (Eq. (2)). In addition, the *in situ* formed alkyl radical was trapped by 1,1-diphenylethylene (**4**), forming the adduct **5** in small quantities (Eq. (3)).





Conclusion

In summary, we have identified a practical approach for the preparation of β , γ -unsaturated carbonyl compounds, by nickel-catalyzed reductive coupling of two easily accessible C–O electrophiles. The method displayed good functional group compatibility for both alkyl oxalates and vinyl triflates. The involvement of alkyl radical intermediates that stems from alkyl oxalates was indicated by control experiments. The enantioconvergent coupling proceeded moderately with low enantiomeric excess; hence, further studies will focus on improving the enantiocontrol.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153129.

References

- [1] K.N. Houk, Chem. Rev. 76 (1976) 1-74.
- [2] M. Iwasaki, E. Morita, M. Uemura, H. Yorimitsu, K. Oshima, Synlett 2007 (2007) 167–169.
- [3] For organocatalysis: H. Kim, D.W.C. MacMillan J. Am. Chem. Soc. 130 (2008) 398-399.
- [4] (a) For synergistic combination of organocatalysis and copper catalysis: E. Skucas, D.W.C. MacMillan J. Am. Chem. Soc. 134 (2012) 9090–9093;
 (b) J.M. Stevens, D.W.C. MacMillan, J. Am. Chem. Soc. 135 (2013) 11756–11759.
- [5] T. Ankner, C.C. Cosner, P. Helquist, For a review on metal-catalyzed vinylation of enolates, Chem. Eur. J. 19 (2013) 1858–1871.
- [6] (a) For selected examples: A. Chieffi, K. Kamikawa, J. Åhman, J.M. Fox, S.L. Buchwald Org. Lett. 3 (2001) 1897–1900;
 (b) J. Huang, E. Bunel, M.M. Faul, Org. Lett. 9 (2007) 4343–4346;
 (c) M. Gringlumos, T. Angros, T. M. Forster, D. O. Wiest, P. Helquirt, J. Am. Chem.
- (c) M. Grigalunas, T. Ankner, P.-O. Norrby, O. Wiest, P. Helquist, J. Am. Chem. Soc. 137 (2015) 7019–7022.
- [7] C. Qiu, K. Yao, X. Zhang, H. Gong, Org. Biomol. Chem. 14 (2016) 11332-11335.
 [8] (a) X. Dai, N.A. Strotman, G.C. Fu, I. Am. Chem. Soc. 130 (2008) 3302-3303.
- [8] (a) X. Dai, N.A. Strotman, G.C. Fu, J. Am. Chem. Soc. 130 (2008) 3302–3303;
 (b) S. Lou, G.C. Fu, J. Am. Chem. Soc. 132 (2010) 5010–5011;
 (c) Z. Wang, Z.-P. Yang, G.C. Fu, Nat. Chem. 13 (2021) 236–242.
- [9] For reviews on transition metal-catalyzed C-O bond cleavage: (a) Cornella, J.; Zarate, C.; Martin, R. Chem. Soc. Rev. 2014, 43, 8081–8097; (b) Su, B.; Cao, Z.-C.; Shi, Z.-J. Acc. Chem. Res. 2015, 48, 886–896; (c) Tollefson, E. J.; Hanna, L. E.; Jarvo, E. R. Acc. Chem. Res. 2015, 48, 2344–2353; (d) Tobisu, M.; Chatani, N. Acc. Chem. Res. 2015, 48, 1717–1726; (e) Zeng, H.; Qiu, Z.; Domínguez-Huerta, A.; Hearne, Z.; Chen, Z.; Li, C. J. ACS Catal. 2017, 7, 510–519.
- [10] X.-B. Yan, C.-L. Li, W.-J. Jin, P. Guo, X.-Z. Shu, Chem. Sci. 9 (2018) 4529-4534.
- [11] (a) Y. Ye, H. Chen, J.L. Sessler, H. Gong, J. Am. Chem. Soc. 141 (2019) 820–824;
 (b) M. Gao, D. Sun, H. Gong, Org. Lett. 21 (2019) 1645–1648.
- [12] For reviews on nickel-catalyzed reductive coupling reactions: (a) Knappke, C. E. I.; Grupe, S.; Gartner, D.; Corpet, M.; Gosmini, C.; Jacobi von Wangelin, A. Chem. Eur. J. 2014, 20, 6828–6842; (b) Moragas, T.; Correa, A.; Martin, R. Chem. Eur. J. 2014, 20, 8242–8258; (c) Everson, D. A.; Weix, D. J. Org. Chem. 2014, 79, 4793–4798; (d) Gu, J.; Wang, X.; Xue, W.; Gong, H. Org. Chem. Front. 2015, 3, 1411–1421; (e) Weix, D. J. Acc. Chem. Res. 2015, 48, 1767–1775; (f) Liu, J.; Ye, Y.; Sessler, J. L.; Gong, H. Acc. Chem. Res. 2020, 53, 1833–1845; (g) Poremba, K. E.; Dibrell S. E.; Reisman, S. E. ACS Catal. 2020, 10, 8237–8246; (h) Xue, W.; Jia, X.; Wang, X.; Tao, X.; Yin, Z.; Gong, H. Chem. Soc. Rev. 2021,50, 4162–4184.
- [13] The role of MgCl2 has been investigated in previous research, see ref.11. It was found that MgCl2 can activate the oxalate and also stabilize the in situ formed radical anion intermediate by the chelation effect, which in turn promotes the single electron transfer reduction of oxalate by Zn.
- [14] For a review on reductive coupling reactions using vinyl electrophiles: Pang, X.; Peng, X.; Shu, X.-Z. Synthesis 2020, 52, 3751–3763.
- [15] For selected examples of vinyl triflates in nickel catalysis: (a) Hofstra, J. L.; Poremba, K. E.; Shimozono, A. M.; Reisman, S. E. Angew. Chem. Int. Ed. 2019, 58, 14901–14905; (b) Tian, Z.-X.; Qiao, J.-B.; Xu, G.-L.; Pang, X.; Qi, L.; Ma, W.-Y.; Zhao, Z.-Z.; Duan, J.; Du, Y.-F.; Su, P.; Liu, X.-Y.; Shu, X.-Z. J. Am. Chem. Soc. 2019, 141, 7637–7643; (c) Pan, F.-F.; Guo, P.; Li, C.-L.; Su, P.; Shu, X.-Z. Org. Lett. 2019, 21, 3701–3705; (d) Qiao, J.-B.; Zhao, Z.-Z.; Zhang, Y.-Q.; Yin, K.; Tian, Z.-X.; Shu, X.-Z. Org. Lett. 2020, 22, 5085–5089.