



Communication

Rh(I)-catalyzed regio- and enantioselective allylic alkylation of Meldrum's acid

Min Liu^a, Haiying Zhao^{a,*}, Changkun Li^{b,*}^a Inner Mongolia Key Laboratory of Fine Organic Synthesis, College of Chemistry and Chemical Engineering, Inner Mongolia University, Hohhot 010021, China^b Shanghai Key Laboratory for Molecular Engineering of Chiral Drugs, School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, Shanghai 200240, China

ARTICLE INFO

Article history:

Received 24 March 2020

Received in revised form 30 March 2020

Accepted 6 April 2020

Available online 14 April 2020

Keywords:

Rhodium

Bisoxazolinephosphine

Allylic substitution

Meldrum's acid

Asymmetric catalysis

ABSTRACT

A Rh(I)-catalyzed highly regio- and enantioselective allylic alkylation of Meldrum acid with racemic allylic substrates bearing alkyl groups has been developed. The applying of chiral bisoxazolinephosphine ligand is essential for the high yields and selectivities. This method provides a rapid access to various chiral β -alkyl- γ,δ -unsaturated carboxylic acids and their derivatives.

© 2020 Chinese Chemical Society and Institute of Materia Medica, Chinese Academy of Medical Sciences. Published by Elsevier B.V. All rights reserved.

Meldrum's acid is a very useful molecule in organic synthesis for its versatile transformation by its strong nucleophilicity and electrophilicity [1]. Due to the easy transformation to acetic acid derivatives by losing CO₂ and acetone, many asymmetric carbon-carbon bond formation reactions have been realized with Meldrum's acid as the carbon nucleophile [2]. Nevertheless, the utilization of Meldrum's acid in the asymmetric allylic substitution reactions is much underexplored [3], which is on sharp contrast to extensively application of malonates as carbon nucleophiles (Scheme 1a). To the best of our knowledge, only two examples have been reported in literature. Kitamura developed a Ru(II)-catalyzed highly branch- and enantioselective allylic alkylation of Meldrum's acid, in which aryl group substituted allylic alcohols could be successfully used (Scheme 1b) [4a,b]. Trost reported a single example with Morita-Baylis-Hillman adduct as substrate [4c]. The reactions from aliphatic group substituted allylic precursors have never been reported.

Our group has developed the earth-abundant first-row cobalt-catalyzed highly regio- and enantioselective allylic amination reaction [5]. The racemic allylic carbonates bearing simple alkyl groups are successfully used in this transformation. The applying of chiral bisoxazolinephosphine ligand is the key to control the selectivities. Recently, we found that the replacement of cobalt by

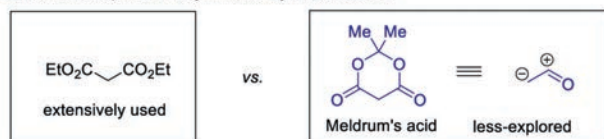
rhodium could further extend the scope to other carbon, oxygen, nitrogen and sulphur pronucleophiles and provide a general reaction platform for different nucleophiles [6]. Herein, we report a Rh(I)-catalyzed regio- and enantio-selective allylic alkylation of Meldrum acid with racemic allylic substrates bearing alkyl groups. β -Alkyl- γ,δ -unsaturated carboxylic acid and its derivatives could be synthesized in up to 83% yield and 99% *ee* (Scheme 1c).

We commenced the study with racemic allylic *t*-butyl carbonate **1a** and Meldrum's acid **2a** as the model substrates (Table 1). A variety of chiral bisoxazolinephosphine ligands were examined in the presence of 2.5 mol% of [Rh(cod)Cl]₂ in toluene at room temperature. The R² group on the oxazoline ring has a profound effect on the reactivity and enantioselectivity of the product **3a**. Reaction with **L1** bearing a small methyl group leads to 29% yield and 53% *ee* (entry 1). The *ee* increases to 96% when the methyl was replaced by *t*-butyl or phenyl group, while the conversions remain low (**L2** and **L3**, entries 2 and 3). To our delight, **L4** with an isopropyl group on the oxazoline ring could help give a 70% yield and 97% *ee* for **3a** (entry 4). The reactions in other solvents gave lower yields, which indicates less polar solvents are benefit for the conversion (entries 5–8). We then examined the substituent effect of R¹ in the ligands. Applying of **L5** with an electron-donating 4-MeOC₆H₄ group could further improve the yield to 85% (entry 9). While, **L6** and **L7** with 4-NMe₂C₆H₄ and 4-MeO-3,5-^tBu₂C₆H₂ groups respectively are not as good as the **L5**, probably due to the relatively bigger size (entries 10 and 11). As predicted, a lower 48% yield was obtained when **L8** with an electron-withdrawing

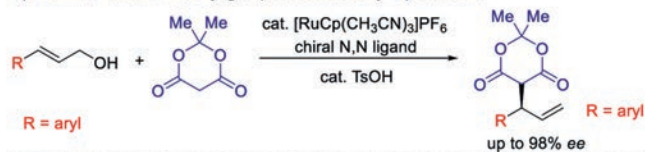
* Corresponding authors.

E-mail addresses: hyzhao@imu.edu.cn (H. Zhao), chkli@sjtu.edu.cn (C. Li).

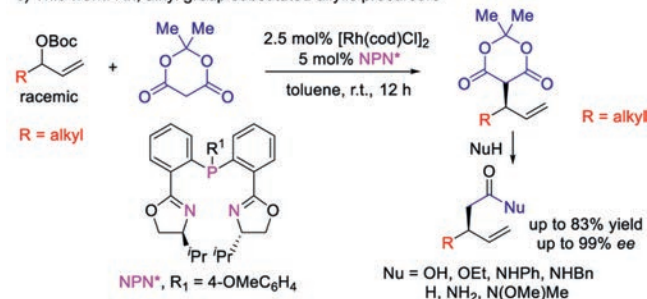
a) Carbon nucleophiles in asymmetric allylic substitution



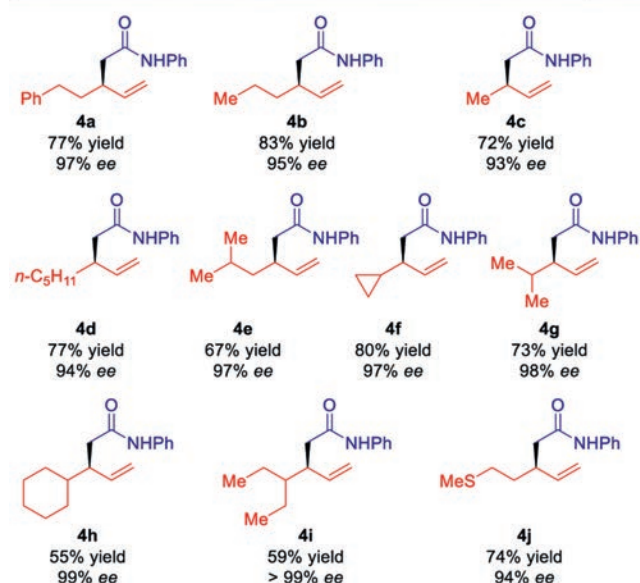
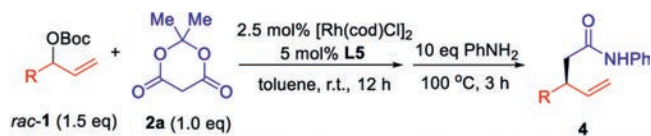
b) Kitamura's work: Ru, aryl group substituted allylic precursors



c) This work: Rh, alkyl group substituted allylic precursors

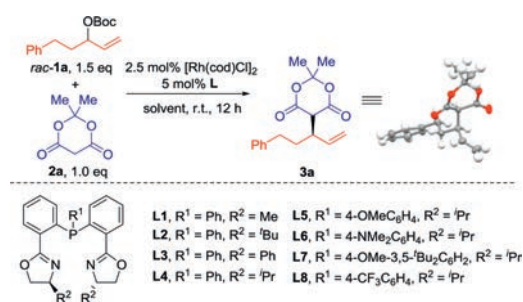


Scheme 1. Asymmetric allylic substitution with Meldrum's acid.



Scheme 2. Reaction scope.

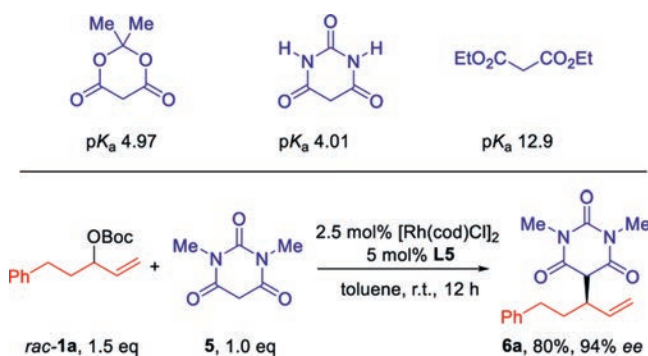
Table 1

Optimization of Rh-catalyzed asymmetric allylic alkylation of Meldrum's acid.^a

Entry	Solvent	Ligand	Yield (%) ^b	ee (%) ^c
1	Toluene	L1	29	53
2	Toluene	L2	18	96
3	Toluene	L3	30	96
4	Toluene	L4	70	97
5	CH ₃ CN	L4	27	95
6	DCM	L4	12	97
7	EtOH	L4	51	99
8	Dioxane	L4	56	96
9	Toluene	L5	85	96
10	Toluene	L6	73	97
11	Toluene	L7	66	99
12	Toluene	L8	48	97
13 ^d	Toluene	L5	< 5	–

^a All reactions were run on a 0.2 mmol scale at 23 °C for 12 h unless otherwise noted.^b Yield of isolated product.^c The ee value was determined by HPLC with chiral column.^d With 5 mol% Rh(cod)₂BF₄.

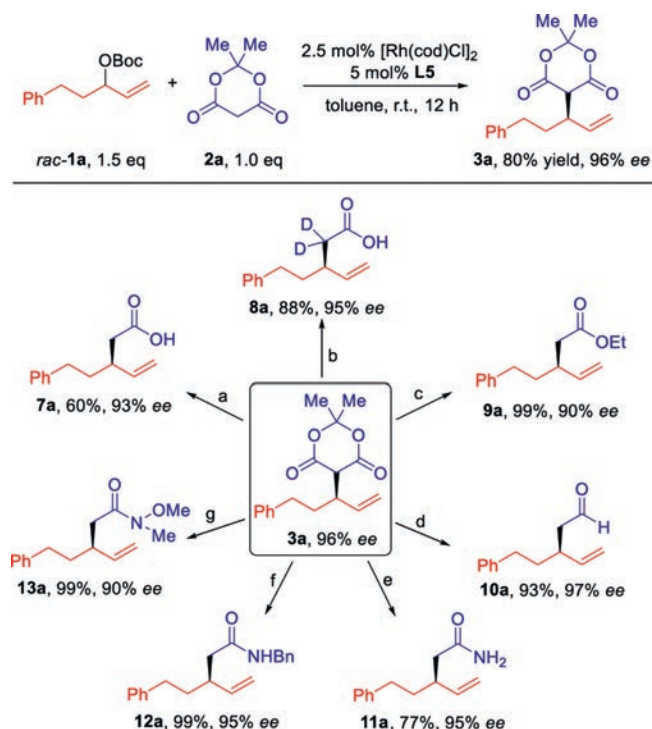
CF₃-C₆H₄ group was used (entry 12). The reaction with 5 mol% Rh(cod)₂BF₄ gave no any product **3a**, which suggests the chloride anion plays a key role in the reaction (entry 13). In all cases, no trace of the linear isomer of **3a** or diallylation product could be

Scheme 3. The pK_a value and the reaction of barbituric acid.

observed [7]. The absolute configuration of **3a** was assigned to be R by single crystal X-ray diffraction analysis of **3a** (CCDC: 1987520).

With the optimal condition in hand (entry 9, Table 1), we examine the scope of allylic carbonates in this highly regio- and enantioselective allylic alkylation reaction (Scheme 2). For the easy determination of the ee values of the products, all the synthesized Meldrum's acid derivatives react further with aniline to give the β-alkyl-γ,δ-unsaturated amide, in which a UV-active phenyl group exists [8]. Allylic carbonates bearing phenylethyl, n-propyl, methyl and n-pentyl groups could be converted to allylation products **4a** to **4d** smoothly. Lower yield of **4e** bearing β-branched methyl group could be obtained. **4f** and **4g** bearing α-branch cyclopropyl and isopropyl groups respectively were synthesized in high yields. The reaction efficiency of **1h** and **1i** with big cyclohexyl and 3-pentyl groups drops, while the enantioselectivities increase to 99% (**4h** and **4i**). Alkyl group with a sulphide function could be well tolerated in this reaction (**4j**). The reaction of phenyl group substituted racemic allylic carbonates gave 70% yield and 53% ee.

The scope of the nucleophile was then checked. 5-Substituted Meldrum's acid is not active in this reaction for the steric reason. Diethyl malonate, the open chain analogue of Meldrum's acid, cannot react as a nucleophile under the identical condition,

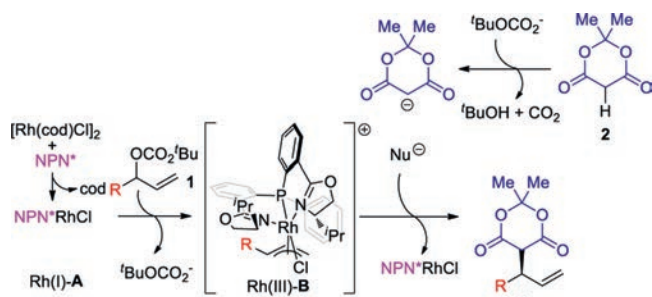


Scheme 4. The synthetic transformation of the Meldrum's acid derivatives. (a) Et₃N (3.0 equiv.), H₂O (10 equiv.), toluene, 110 °C, 3 h; (b) D₂O (10 equiv.), pyridine, 100 °C, 5 h; (c) Et₃N (3.0 equiv.), EtOH (5 equiv.), toluene, 110 °C, 3 h; (d) Et₃N (4.0 equiv.), PhSiH₃ (3 equiv.), THF, r.t., 2 h; (e) NH₃·H₂O (5.0 equiv.), toluene, 110 °C, 3 h; (f) BnNH₂ (5.0 equiv.), toluene, 110 °C, 3 h; (g) HCl·HN(OMe)Me (2.0 equiv.), toluene, 110 °C, 3 h.

probably due to its much lower acidity. Considering the similarity of barbituric acid's pK_a value (4.01), 1,3-dimethylbarbituric acid **5** readily reacts to give **6a** in 80% yield and 94% ee (Scheme 3) [9].

The Meldrum's acid derivative **3a** bearing a chiral allyl group was synthesized in 80% yield (Scheme 4). **3a** could be transformed into the free carboxylic acid **7a** [8] and the α -deuterated **8a** [10] easily by treatment with Et₃N or pyridine in water (D₂O) (routes a and b). The corresponding ethyl ester **9a** was synthesized similarly by reaction with ethanol and Et₃N in 99% yield (route c) [2d]. The substituted Meldrum's acid **3a** was readily reduced by Et₃N and PhSiH₃ to aldehyde **10a** in 93% yield, without any erosion of the enantioselectivity (route d) [11]. Not only aniline, NH₃·H₂O and aliphatic benzylamine could also react with **3a** to prepare the primary and secondary amide **11a** [12] and **12a** [13]. Finally, Weinreb amide **13a** was synthesized in high yield, which allows the ketone synthesis by reaction further with organometallic reagents [8].

Based on the experiments above and the literature reports, plausible mechanism was proposed as shown in Scheme 5. The



Scheme 5. Proposed mechanism.

in-situ formed NPN*RhCl (Rh(I)-A) reacts with the allylic *t*-butyl carbonate **1** to get the chiral cationic intermediate Rh(III)-B as a 18 electron complex. At the same time *t*-butyl carbonate anion was released as the counter anion [14]. The catalytic amount of basic *t*-butyl carbonate anion removes the acidic proton in the pronucleophile **2** to generate the Meldrum's acid anion and release neutral *t*-butanol and CO₂, which enables the reaction conduction in base-free condition, while the less acidic diethyl malonate could not be deprotonated and react under the same condition. When Rh(cod)₂BF₄ was used as the rhodium precursor, *t*-butyl carbonate anion binds with rhodium and no free base is available to activate the Meldrum's acid. Finally, the nucleophile attacks the chiral Rh(III)-B intermediate from the bottom side regio- and enantioselectively via an outer-sphere mechanism to give **3** and release NPN*RhCl catalyst.

In conclusion, we have developed the Rh/bisoxazoline-phosphine-catalysed highly branched and enantioselective allylic alkylation of Meldrum's acid. Simple alkyl group based allylic precursors are utilized for the first time in the allylic alkylation of Meldrum's acid. The chiral Meldrum's acid derivatives could be converted to β -alkyl- γ,δ -unsaturated carboxylic acid and its derivatives [15]. Further extension of novel nucleophiles in this Rh-catalysed regio- and enantioselective allylic alkylation reaction is under investigation.

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

This work was financially supported by the National Natural Science Foundation of China (NSFC, Nos. 21602130 and 21961023) and the startup funding from Shanghai Jiao Tong University.

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.2020.04.009.

References

- [1] A.M. Dumas, E. Fillion, Acc. Chem. Res. 43 (2010) 440–454.
- [2] (a) B.M. Trost, C. Jäkel, B. Plietker, J. Am. Chem. Soc. 125 (2003) 4438–4439; (b) B.M. Trost, A.B.C. Simas, B. Plietker, C. Jäkel, J. Xie, Chem. Eur. J. 11 (2005) 7075–7082; (c) N.G. Adamson, K.C.E. Wilbur, S.J. Malcolmson, J. Am. Chem. Soc. 140 (2018) 2761–2764; (d) T.M. Khopade, T.B. Mete, J.S. Arora, R.G. Bhat, Chem. Eur. J. 24 (2018) 6036–6040; (e) K.L. Kimmel, J.D. Weaver, J.A. Ellman, Chem. Sci. 3 (2012) 121–125; (f) C. Wang, L.A. Chen, H. Huo, et al., Chem. Sci. 6 (2015) 1094–1100.
- [3] (a) U. Kazmaier, Transition Metal Catalyzed Enantioselective Allylic Substitution in Organic Synthesis, Springer Verlag, Berlin and Heidelberg, 2012; (b) B.M. Trost, D.L. Van Vranken, Chem. Rev. 96 (1996) 395–422; (c) B.M. Trost, M.L. Crawley, Chem. Rev. 103 (2003) 2921–2943; (d) Z. Lu, S. Ma, Angew. Chem. Int. Ed. 47 (2008) 258–297; (e) Q. Cheng, H.F. Tu, C. Zheng, et al., Chem. Rev. 119 (2019) 1855–1969.
- [4] (a) K. Miyata, H. Kutsuna, S. Kawakami, M. Kitamura, Angew. Chem. Int. Ed. 50 (2011) 4649–4653; (b) K. Miyata, M. Kitamura, Synthesis 44 (2012) 2138–2146; (c) B.M. Trost, M.K. Brennan, Org. Lett. 9 (2007) 3961–3964.
- [5] S. Ghorai, S.S. Chirke, W.B. Xu, J.F. Chen, C. Li, J. Am. Chem. Soc. 141 (2019) 11430–11434.
- [6] (a) W.B. Xu, S. Ghorai, W. Huang, C. Li, ACS Catal. 10 (2020) 4491–4496; (b) S.B. Tang, X. Zhang, H.F. Tu, S.L. You, J. Am. Chem. Soc. 140 (2018) 7737–7742; (c) B.W.H. Turnbull, P.A. Evans, J. Org. Chem. 83 (2018) 11463–11479;

- (d) M.B. Thoke, Q. Kang, *Synthesis* 51 (2019) 2585–2631;
(e) P. Koschker, B. Breit, *Acc. Chem. Res.* 49 (2016) 1524–1536.
- [7] (a) K. Manabe, S. Kobayashi, *Org. Lett.* 5 (2003) 3241–3244;
(b) F.X. Felpin, Y. Landais, *J. Org. Chem.* 70 (2005) 6441–6446.
- [8] S. Mishra, J. Liu, A. Aponick, *J. Am. Chem. Soc.* 139 (2017) 3352–3355.
- [9] (a) M. Rombola, C.S. Sumaria, T.D. Montgomery, V.H. Rawal, *J. Am. Chem. Soc.* 139 (2017) 5297–5300;
(b) Y. Liu, Y. Zhang, H.X. Duan, D.Y. Wanyan, Y.Q. Wang, *Org. Biomol. Chem.* 15 (2017) 8669–8679.
- [10] S.P. Andrews, M. Ladlow, *J. Org. Chem.* 68 (2003) 5525–5533.
- [11] C.G. Frost, B.C. Hartley, *J. Org. Chem.* 74 (2009) 3599–3602.
- [12] X. Lei, J.A. Porco Jr., *Org. Lett.* 6 (2004) 795–798.
- [13] S.A. Adediran, D. Cabaret, J.F. Lohier, M. Wakselman, R.F. Pratt, *Bioorg. Med. Chem.* 18 (2010) 282–291.
- [14] (a) J. Tsuji, I. Shimazu, I. Minami, Y. Ohashi, *Tetrahedron Lett.* 23 (1982) 4809–4812;
(b) J. Tsuji, I. Shimazu, I. Minami, et al., *J. Org. Chem.* 50 (1985) 1523–1529.
- [15] (a) Y. Sempere, E.M. Carreira, *Angew. Chem. Int. Ed.* 57 (2018) 7654–7658;
(b) Y. Sempere, J.L. Alfke, S.L. Rossler, E.M. Carreira, *Angew. Chem. Int. Ed.* 58 (2019) 9537–9541.