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Organocatalytic asymmetric domino Michael/O-alkylation reaction for the construction of succinimide substituted 3(2*H*)-furanones catalyzed by quinine†

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A new organocatalytic asymmetric domino Michael/O-alkylation reaction of maleimides with γ -halogenated- β -ketoesters catalyzed by simple, cheap, and commercially available quinine is described. The substrates are also commercially available. A variety of new chiral succinimide substituted 3(2*H*)-furanones were obtained in high yields (up to 94%) and good enantioselectivities (up to 94% ee). The absolute configuration of the new compound **4f** was determined by single-crystal X-ray analysis and the proposed reaction pathway is also shown.

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3(2*H*)-Furanones are core structural motifs that are widely present in many natural products and medicinally important agents.¹ 3(2*H*)-Furanone derivatives exhibit a wide range of biological activities such as antiulcer,² antitumor,³ antiallergic,⁴ antiproliferative,⁵ selective MAO-B inhibitory⁶ and selective COX-2 inhibitory⁷ activities. A variety of approaches toward the synthesis of achiral 3(2*H*)-furanones have been established, including metal-free processes⁸ as well as transition-metal-catalyzed cyclizations.⁹ However, protocols to construct chiral 3(2*H*)-furanone derivatives have been less studied. Marson and coworkers reported Sharpless's asymmetric dihydroxylation followed by a cyclization sequence of enynones to synthesize chiral 3(2*H*)-furanones.¹⁰ Jing and coworkers reported asymmetric Michael addition of simple 3(2*H*)-furanones to α,β -unsaturated ketones catalyzed by a cinchona-based tertiary-primary diamine catalyst¹¹ or α,β -unsaturated aldehydes catalyzed by diphenylprolinol silyl ether¹² to construct complex chiral 3(2*H*)-furanones. These reactions require harsh reaction conditions or specific substrates and complex chiral catalysts. Recently, γ -halogenated- β -ketoesters, which are commercially available, are used to construct chiral 3(2*H*)-furanones with imines¹³ and chain nitroalkenes¹⁴ *via* domino reactions.¹⁵ This synthetic strategy is efficient and mild. However, these reactions also need complex chiral catalysts such as tertiary amine squaramide,^{13a} tertiary amine thiourea^{13b,14a} and 6'-demethyl quinine catalysts.^{14b} Moreover, the substrate scope is relatively

limited. For the significance of chiral 3(2*H*)-furanones, it is strongly useful and desirable to discover other appropriate electrophiles such as cyclic alkenes to react with γ -halogenated- β -ketoesters catalyzed by simple, cheap, commercially available catalysts to construct diverse chiral substituted 3(2*H*)-furanones.

Maleimides, which are also commercially available, are an important class of cyclic alkenes. They have been extensively applied in asymmetric organocatalysis to construct chiral succinimide derivatives, which are core structural units found in natural products and clinical drug candidates.¹⁶ To date, there has been no report of asymmetric reaction of γ -halogenated- β -ketoesters with maleimides, which could afford a new class of chiral products combining biologically significant succinimides with 3(2*H*)-furanones. These fused chiral products might show higher or new biological activities. Recently, we reported the same transformation in racemic version catalyzed by Et₃N.¹⁷ As a part of our continuing interests in the construction of more complex and novel drug candidates,¹⁸ herein, we wish to report the first asymmetric domino Michael/O-alkylation reaction of γ -halogenated- β -ketoesters with maleimides catalyzed by simple, cheap, commercially available cinchona alkaloids to access a new range of chiral succinimide substituted 3(2*H*)-furanones (Fig. 1). Córdova and coworkers reported asymmetric domino Michael/ α -alkylation reaction of γ -halogenated- β -ketoesters with α,β -unsaturated aldehydes to afford cyclopentanone products.¹⁹ This report shows variable chemical reactivities of γ -halogenated- β -ketoesters with activated alkenes. Our preliminary studies involved maleimide **1a** and ethyl 4-bromo-acetoacetate **2a** as substrates, these were allowed to react in the presence of 20 mol% cinchonine with 100 mol% Na₂CO₃ in CH₂Cl₂ at room temperature. The reaction worked

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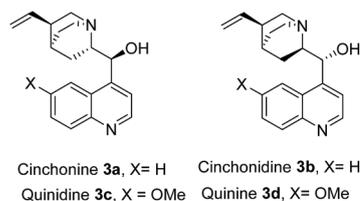


Fig. 1 Screened catalysts.

well and gave succinimide substituted 3(2*H*)-furanone **4a** in 85% yield and 68% ee *via* domino Michael/O-alkylation process not Michael/ α -alkylation process (Scheme 1).

To evaluate the reactivity of this catalytic system, the reaction of *N*-phenyl maleimide **1a** with ethyl 4-bromo-acetoacetate **2a** was used as a model reaction, and four kinds of natural cinchona alkaloid catalysts were investigated in CH₂Cl₂ at room temperature (Table 1, entries 1–4). All catalysts gave good yields, quinine afforded best enantioselectivity than other catalysts and was chosen as the most suitable catalyst for further optimization (Table 1, entry 4). Then an array of base additives were screened (Table 1, entries 4–6). Organic base Et₃N afforded good yield but poor enantioselectivity (Table 1, entry 5). Weak inorganic base NaHCO₃ decreased the reaction rate, afforded poor yield after reaction for 24 h (Table 1, entry 6). Inorganic base Na₂CO₃ afforded good yield and moderate enantioselectivity after reaction for 10 h. In terms of yields and enantioselectivities, Na₂CO₃ was chosen as the most suitable base additive for further optimization (Table 1, entry 4). Afterward, a series of solvents were evaluated (Table 1, entries 7–13). Halohydrocarbon solvents afforded good yield and moderate enantioselectivity (Table 1, entry 7). THF and toluene gave lower yields and enantioselectivities (Table 1, entries 9 and 10). Et₂O gave poor yield (Table 1, entry 8) and *n*-hexane gave trace product (Table 1, entry 13), the possible reason might be the poor solubility of the raw materials and catalyst in these solvents. Polar solvents such as EtOAc and acetonitrile gave good yields and poor enantioselectivities (Table 1, entries 11 and 12). A survey of solvents revealed that CHCl₃ was the most suitable solvent (Table 1, entry 7).

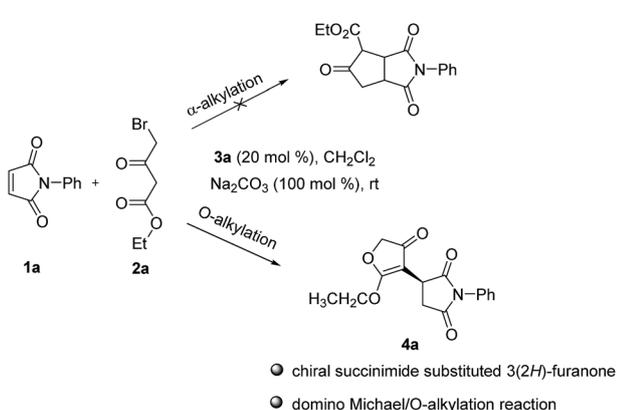
To further optimize the reaction conditions, reaction temperature was investigated (Table 2, entries 1–4). Decreasing reaction temperature increased enantioselectivities but slowed down the reaction rate. After reaction for 24 h, good yield could still be obtained at 0 °C (Table 2, entry 2), but further lowering the reaction temperature, the yields decreased obviously (Table 2, entries 3 and 4). 0 °C was the optimal reaction temperature. Then we examined the effect of catalyst loadings. Decreasing catalyst loadings to 10 mol% still gave good yield and enantioselectivity (Table 2, entry 5). We next examined the effect of molar ratio, increasing or lowering the molar ratio slightly influenced the yields and slightly decreased the enantioselectivities (Table 2, entries 6 and 7). The substrate concentration was also examined. It was found that increasing or lowering the substrate concentration slightly decreased the yields and enantioselectivities (Table 2, entries 8 and 9). Consequently, the following reaction conditions were recommended: 10 mol% quinine, 1 equivalent of Na₂CO₃ with 0.2 M of substrate concentration in CHCl₃ at 0 °C.

Under the optimal reaction conditions, the generality of this protocol was studied (Table 3). Firstly, a wide range of *N*-aromatic and aliphatic maleimides **1a–m** were studied (Table 3, entries 1–13). All gave good yields and moderate to good enantioselectivities (80–94% yield, 68–94% ee). *N*-phenyl maleimides with strong electron-withdrawing nitro group **1g** and **1i** gave slightly lower yields and enantioselectivities (Table 3, entries 7 and 9). For *N*-aliphatic maleimides, good yields and enantioselectivities could still be obtained (Table 3, entries 11–13) and *N*-benzyl maleimide gave best enantioselectivity (91% yield, 94% ee, Table 3, entry 13). In addition, methyl 4-chloroacetoacetate **2b** and ethyl 4-bromoacetoacetate **2c** were

Table 1 Optimization of reaction conditions^a

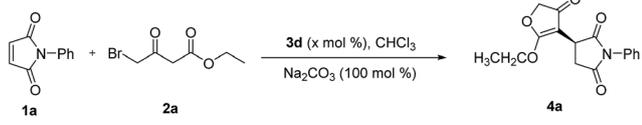
Entry	Cat.	Base	Solvent	Time (h)	Yield ^b (%)	ee ^c (%)
1	3a	Na ₂ CO ₃	CH ₂ Cl ₂	10	85	68 ^d
2	3b	Na ₂ CO ₃	CH ₂ Cl ₂	10	83	64
3	3c	Na ₂ CO ₃	CH ₂ Cl ₂	10	86	68 ^d
4	3d	Na ₂ CO ₃	CH ₂ Cl ₂	10	88	71
5	3d	Et ₃ N	CH ₂ Cl ₂	2	92	49
6	3d	NaHCO ₃	CH ₂ Cl ₂	24	49	74
7	3d	Na ₂ CO ₃	CHCl ₃	10	90	75
8	3d	Na ₂ CO ₃	Et ₂ O	10	68	52
9	3d	Na ₂ CO ₃	THF	10	82	47
10	3d	Na ₂ CO ₃	Toluene	10	80	68
11	3d	Na ₂ CO ₃	EtOAc	10	84	19
12	3d	Na ₂ CO ₃	CH ₃ CN	10	89	12
13	3d	Na ₂ CO ₃	<i>n</i> -Hexane	10	Trace	nd

^a Unless otherwise noted, reactions were conducted with 0.2 mmol **1a**, 0.2 mmol **2a**, 20 mol% catalyst **3**, 100 mol% base, in 1.0 mL solvent at rt. ^b Isolated yields. ^c Determined by chiral HPLC analysis. ^d Contrary configuration.



Scheme 1 Asymmetric domino Michael/O-alkylation reaction.



Table 2 Optimization of reaction conditions^a


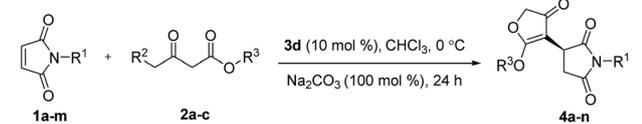
Entry	Temp (°C)	x	Time (h)	Yield ^b (%)	ee ^c (%)
1	25	20	10	90	75
2	0	20	24	91	83
3	-10	20	24	72	84
4	-20	20	24	67	85
5	0	10	24	89	83
6 ^d	0	10	24	87	82
7 ^e	0	10	24	92	80
8 ^f	0	10	24	88	79
9 ^g	0	10	24	86	82

^a Unless otherwise noted, reactions were conducted with 0.2 mmol **1a**, 0.2 mmol **2a**, catalyst **3d**, 100 mol% Na₂CO₃, in 1.0 mL CHCl₃.

^b Isolated yields. ^c Determined by chiral HPLC analysis. ^d 1.5 equivalents **1a** was used. ^e 1.5 equivalents **2a** was used. ^f 0.5 mL CHCl₃ was used. ^g 2.0 mL CHCl₃ was used.

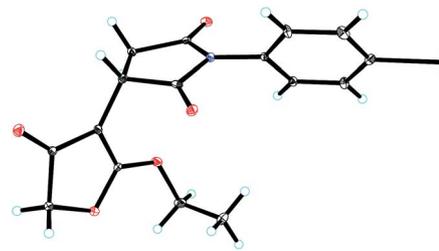
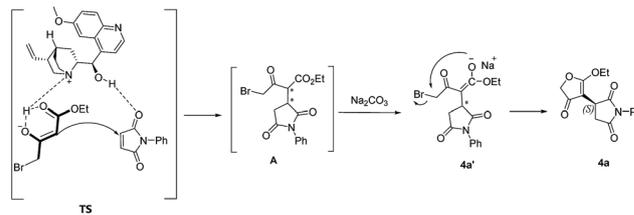
also tested, both provided good yields and enantioselectivities (Table 3, entries 14 and 15). The absolute configuration was determined by an X-ray analysis of the single crystal of **4f**, which was assigned as (S) (Fig. 2).²⁰

Based on the experimental results and the observed configuration of **4f**, a plausible mechanism is proposed in Scheme 2.^{18a} The tertiary amine group of quinine catalyst activates 4-bromo-

Table 3 Scope of substrates^a


Entry	1/R ¹	2/R ² , R ³	4	Yield ^b (%)	ee ^c (%)
1	1a /C ₆ H ₅	2a /Br, Et	4a	89	83
2	1b /4-CH ₃ C ₆ H ₄	2a /Br, Et	4b	93	83
3	1c /4-CH ₃ OC ₆ H ₄	2a /Br, Et	4c	90	87
4	1d /4-FC ₆ H ₄	2a /Br, Et	4d	87	80
5	1e /4-ClC ₆ H ₄	2a /Br, Et	4e	92	84
6	1f /4-BrC ₆ H ₄	2a /Br, Et	4f	88	83
7	1g /4-NO ₂ C ₆ H ₄	2a /Br, Et	4g	84	77
8	1h /3-FC ₆ H ₄	2a /Br, Et	4h	87	79
9	1i /3-NO ₂ C ₆ H ₄	2a /Br, Et	4i	82	68
10	1j /2-MeC ₆ H ₄	2a /Br, Et	4j	80	83
11	1k /CH ₃	2a /Br, Et	4k	94	72
12	1l /Cyclohexyl	2a /Br, Et	4l	85	89
13	1m /Bn	2a /Br, Et	4m	91	94
14	1a /C ₆ H ₅	2b /Cl, Me	4n	86	78
15	1a /C ₆ H ₅	2c /Cl, Et	4a	83	80

^a Unless otherwise noted, reactions were conducted with 0.2 mmol **1a**, 0.2 mmol **2a**, 10 mol% catalyst **3d**, 100 mol% Na₂CO₃, in 1.0 mL CHCl₃ at 0 °C. ^b Isolated yields. ^c Determined by chiral HPLC analysis.

Fig. 2 X-ray crystal structure of product **4f**.

Scheme 2 Proposed mechanism.

acetoacetate in its enol form and the hydroxyl moiety activates maleimide through hydrogen bonding, thus the enolate would attack the maleimide from Re face *via* transition state TS (Scheme 2). Through the dual activation of quinine catalyst, Michael reaction is realized and generates intermediary Michael adduct **A**. Then in the presence of Na₂CO₃, intermediary Michael adducts **A** forms enolate ion **4a'**, which undergoes an intramolecular O-alkylation process to form the product **4a** with (S)-configuration.

Conclusions

In summary, we have developed a new organocatalytic asymmetric domino Michael/O-alkylation reaction of maleimides with γ -halogenated- β -ketoesters catalyzed by simple, cheap, and commercially available quinine. The substrates are also commercially available. A wide range of new chiral succinimide substituted 3(2*H*)-furanones were smoothly obtained in high yields (up to 94%) and good enantioselectivities (up to 94% ee). Further, expansion of these new succinimide substituted 3(2*H*)-furanones to access products with known biological activities or new biologically significant molecules and testing their pharmacological activities are ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- Selected examples: (a) Y. Li and K. J. Hale, *Org. Lett.*, 2007, **9**, 1267; (b) J. M. Mitchell and N. S. Finney, *Org. Biomol. Chem.*, 2005, **3**, 4274; (c) Y. Hayashi, M. Shoji, S. Yamaguchi, T. Mukaiyama, J. Yamaguchi, H. Kakeya and H. Osada, *Org. Lett.*, 2003, **5**, 2287; (d) K. Takao, H. Ochiai, K. Yoshida, T. Hashizuka, H. Koshimura, K. Tadano and S. Ogawa, *J. Org. Chem.*, 1995, **60**, 8179; (e) Q. Han and D. F. Wiemer, *J. Am. Chem. Soc.*, 1992, **114**, 7692; (f) A. C. Gyorkos, J. K. Stille and L. S. Hegedus, *J. Am. Chem. Soc.*, 1990, **112**, 8465.
- S. W. Felman, I. Jirkovsky, K. A. Memoli, L. Borella, C. Wells, J. Russell and J. Ward, *J. Med. Chem.*, 1992, **35**, 1183.
- P. J. Jerris and A. B. Smith III, *J. Org. Chem.*, 1981, **46**, 577.
- R. A. Mack, W. I. Zazulak, L. A. Radov, J. E. Baer, J. D. Stewart, P. H. Elzer, C. R. Kinsolving and V. S. Georgiev, *J. Med. Chem.*, 1988, **31**, 1910.
- S. Chimichi, M. Boccalini, B. Cosimelli, F. Dall'Acqua and G. Viola, *Tetrahedron*, 2003, **59**, 5215.
- A. Carotti, A. Carrieri, S. Chimichi, M. Boccalini, B. Cosimelli, C. Gnerre, A. Carotti, P. A. Carrupt and B. Testa, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 3551.
- J. L. Shamshina and T. S. Snowden, *Tetrahedron Lett.*, 2007, **48**, 3767.
- Selected examples: (a) S. Inagaki, M. Ukaku, A. Chiba, F. Takahashi, Y. Yoshimi, T. Morita and T. Kawano, *J. Org. Chem.*, 2016, **81**, 8363; (b) J. J. Medvedev, D. V. Semenok, X. V. Azarova, L. L. Rodina and V. A. Nikolaev, *Synthesis*, 2016, **48**, 4525; (c) A. G. Mal'kina, O. G. Volostnykh, K. B. Petrusenko, O. A. Shemyakina, V. V. Nosyreva, I. A. Ushakov and B. A. Trofimov, *Tetrahedron*, 2013, **69**, 3714; (d) Y. Wei, S.-X. Lin, J. Zhang, Z.-H. Niu, Q. Fu and F.-S. Liang, *Chem. Commun.*, 2011, **47**, 12394; (e) Y. Wei, S.-X. Lin, H.-X. Xue, F.-S. Liang and B.-Z. Zhao, *Org. Lett.*, 2012, **14**, 712; (f) G.-Q. Yuan, Z.-J. He, J.-H. Zheng, Z.-W. Chen, H.-W. Huang, D.-B. Shi, C.-R. Qi and H.-F. Jiang, *Tetrahedron Lett.*, 2011, **52**, 5956.
- Selected examples: (a) H.-T. He, C.-R. Qi, X.-H. Hu, L. Ouyang, W.-F. Xiong and H.-F. Jiang, *J. Org. Chem.*, 2015, **80**, 4957; (b) J. John, E. Târcoveanu, P. G. Jones and H. Hopf, *Beilstein J. Org. Chem.*, 2014, **10**, 1462; (c) J. John and H. Hopf, *Eur. J. Org. Chem.*, 2013, 841; (d) T. C. Kusakabe, T. Takahashi, R. Shen, A. Ikeda, Y. D. Dhage, Y. Kanno, Y. Inouye, H. Sasai, T. Mochida and K. Kato, *Angew. Chem., Int. Ed.*, 2013, **52**, 1; (e) F. Hu, J.-W. Yan, M. Cheng and Y.-H. Hu, *Chem.-Asian J.*, 2013, **8**, 482; (f) C.-R. Qi, H.-F. Jiang, L.-B. Huang, G.-Q. Yuan and Y.-W. Ren, *Org. Lett.*, 2011, **13**, 5520; (g) M. Poonoth and N. Krause, *J. Org. Chem.*, 2011, **76**, 1934; (h) M. Egi, K. Azechi, M. Saneto, K. Shimizu and S. Akai, *J. Org. Chem.*, 2010, **75**, 2123.
- C. M. Marson, E. Edaan, J. M. Morrell, S. J. Coles, M. B. Hursthouse and D. T. Davies, *Chem. Commun.*, 2007, 2494.
- W.-J. He, L.-H. Jing, D.-B. Qin, R.-M. Wang, X.-H. Xie and S. Wu, *Tetrahedron Lett.*, 2013, **54**, 6363.
- W.-J. He, L.-H. Jing, D.-B. Qin, X.-H. Xie, S. Wu and R.-M. Wang, *Tetrahedron Lett.*, 2014, **55**, 209.
- (a) X.-B. Wang, T.-Z. Li, F. Sha and X.-Y. Wu, *Eur. J. Org. Chem.*, 2014, 739; (b) N.-H. Luo, X. Sun, Y.-Y. Yan, S.-Z. Nie and M. Yan, *Tetrahedron: Asymmetry*, 2011, **22**, 1536.
- (a) X.-W. Dou, X.-Y. Han and Y.-X. Lu, *Chem.-Eur. J.*, 2012, **18**, 85; (b) Y.-Y. Yan, R.-J. Lu, J.-J. Wang, Y.-N. Xuan and M. Yan, *Tetrahedron*, 2012, **68**, 6123.
- Selected examples: (a) L. Liu, Y. Cotelte, J. Klehr, N. Sakai, T. R. Ward and S. Matile, *Chem. Sci.*, 2017, **8**, 3770; (b) A. Bhaumik, R. S. Verma and B. Tiwari, *Org. Lett.*, 2017, **19**, 444; (c) K. Zhao, Y. Zhi, T. Shu, A. Valkonen, K. P. Rissanen and D. Enders, *Angew. Chem., Int. Ed.*, 2016, **55**, 12104; (d) E. S. Diez, D. L. Vesga, E. Reyes, U. Uria, L. Carrillo and J. L. Vicario, *Org. Lett.*, 2016, **18**, 1270.
- Selected examples: (a) R. Huang, H.-Y. Tao and C.-J. Wang, *Org. Lett.*, 2017, **19**, 1176; (b) J. F. Ferrándiz and R. Chinchilla, *Tetrahedron: Asymmetry*, 2017, **28**, 302; (c) C.-C. Zou, C.-K. Zeng, Z. Liu, M. Lu, X.-H. Sun and J.-X. Ye, *Angew. Chem., Int. Ed.*, 2016, **55**, 14257; (d) D. Kalia, P. V. Malekar and M. Parthasarathy, *Angew. Chem., Int. Ed.*, 2016, **55**, 1432; (e) L. Liu, B.-L. Zhao and D.-M. Du, *Eur. J. Org. Chem.*, 2016, **2016**, 4711; (f) S. Qiu, R. Lee, B. Zhu, M. L. Coote, X.-W. Zhao and Z.-Y. Jiang, *J. Org. Chem.*, 2016, **81**, 8061.
- W. Wang, G.-J. Liang, Y. Bai, L.-J. Bai, H. Zhou, Y. Yu and J. Zhou, *ARKIVOC*, 2017, **4**, 236.
- (a) J. Zhou, Q.-L. Wang, L. Peng, F. Tian, X.-Y. Xu and L.-X. Wang, *Chem. Commun.*, 2014, **50**, 14601; (b) J. Zhou, L.-N. Jia, Q.-L. Wang, L. Peng, F. Tian, X.-Y. Xu and L.-X. Wang, *Tetrahedron*, 2014, **70**, 8665; (c) J. Zhou, L.-N. Jia, L. Peng, Q.-L. Wang, F. Tian, X.-Y. Xu and L.-X. Wang, *Tetrahedron*, 2014, **70**, 3478; (d) Q.-L. Wang, T. Cai, J. Zhou, F. Tian, X.-Y. Xu and L.-X. Wang, *Chem. Commun.*, 2015, **51**, 10726; (e) Y.-L. Guo, L.-N. Jia, L. Peng, L.-W. Qi, J. Zhou, F. Tian, X.-Y. Xu and L.-X. Wang, *RSC Adv.*, 2013, **3**, 16973.
- R. Rios, J. Vesely, H. Sundén, I. Ibrahim, G.-L. Zhao and A. Córdova, *Tetrahedron Lett.*, 2007, **48**, 5835.
- The CCDC number is 1524709.†

