ChemComm

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c4cc10343b

Received 27th December 2014,
Accepted 27th January 2015

DOI: 10.1039/c4cc10343b

www.rsc.org/chemcomm

Enantioselective synthesis of dihydrocoumarin derivatives by chiral scandium(III)-complex catalyzed inverse-electron-demand hetero-Diels–Alder reaction†

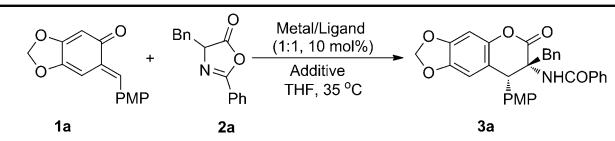
Haipeng Hu,[a] Yangbin Liu,[a] Jing Guo,[a] Lili Lin,[a] Yali Xu,[a] Xiaohua Liu[a] and Xiaoming Feng*[ab]

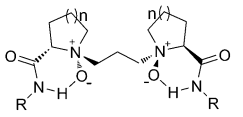
An asymmetric inverse-electron-demand hetero-Diels–Alder reaction between *o*-quinone methides and azlactones to generate potentially pharmacological active dihydrocoumarins has been achieved efficiently by using a chiral *N*,*N*′-dioxide–Sc(III) complex as the catalyst. The desired products were obtained in high yields with excellent enantioselectivities and diastereoselectivities (up to 94% yield, 96% ee and >19 : 1 dr) under mild reaction conditions. A concerted reaction pathway was confirmed by Operando IR and control experiments.

Chiral dihydrocoumarin derivatives have attracted much attention due to their pharmacological and physiological activities such as anti-inflammatory, HIV replication inhibition and antioxidant.[1] Consequently, significant efforts have been devoted to the asymmetric synthesis of these fascinating molecules and many methods have been reported in recent years.[2] Among them, the [4+2] cycloaddition of *ortho*-quinone methides (QMs) with enolates was found to be an efficient way for the synthesis of chiral dihydrocoumarin with continuous stereocenters. In 2008, Lectka reported the [4+2] cycloaddition of QMs with silyl ketene acetals catalyzed by chiral ammonium fluoride, and a stepwise reaction pathway was proposed.[3] Later, Ye's group reported chiral N-heterocyclic carbenes to catalyze the formal [4+2] cycloaddition reaction of QMs and ketenes, affording chiral 3,3,4-trialkyl substituted 3,4-dihydrocoumarins.[4] On the other hand, azlactones involving the nucleophilic C4 and electrophilic C5 could serve as electron-rich dienophiles *via* enolization.[5] However, they have not been employed in the inverse-electron-demand hetero-Diels–Alder (IEDDA)[6] reaction with QMs. What's more, the corresponding products containing a tertiary carbon and a nitrogen atom substituted quaternary stereocenters also exhibit charming biological activities.[7] Herein, we demonstrate a highly efficient IEDDA reaction of QMs with azlactones catalyzed by a chiral *N*,*N*′-dioxide–scandium(III) complex, generating amino substituted 3,4-dihydrocoumarins.

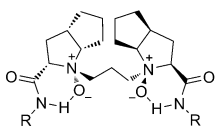
Initially, QM (**1a**) and azlactone (**2a**) were employed as the model substrates, and the reaction was investigated at 35 °C in

Table 1 Optimization of the reaction conditions





L-PrMe$_2$: R = 2,6-Me$_2$C$_6$H$_3$, n = 1
L-PrPr$_2$: R = 2,6-^{i}Pr$_2$C$_6$H$_3$, n = 1
L-PrMe$_2$Bu : R = 2,6-Me$_2$-4-^{t}BuC$_6$H$_2$, n = 1
L-PiMe$_2$Bu : R = 2,6-Me$_2$-4-^{t}BuC$_6$H$_2$, n = 2



L-RaMe$_2$Bu : R = 2,6-Me$_2$-4-^{t}BuC$_6$H$_2$

Entry[a]	Ligand	Metal	Additive	Yield[b] (%)	ee[c] (%)
1	**L-PrMe$_2$**	Ni(OTf)$_2$	—	60	19
2	**L-PrMe$_2$**	Yb(OTf)$_3$	—	54	24
3	**L-PrMe$_2$**	Sc(OTf)$_3$	—	38	74
4	**L-PrPr$_2$**	Sc(OTf)$_3$	—	12	25
5	**L-PrMe$_2$Bu**	Sc(OTf)$_3$	—	<5	80
6	**L-PiMe$_2$Bu**	Sc(OTf)$_3$	—	11	77
7	**L-RaMe$_2$Bu**	Sc(OTf)$_3$	—	14	80
8	**L-RaMe$_2$Bu**	Sc(OTf)$_3$	Na_2CO_3	41	46
9	**L-RaMe$_2$Bu**	Sc(OTf)$_3$	DABCO	38	67
10	**L-RaMe$_2$Bu**	Sc(OTf)$_3$	DMAP	50	88
11	**L-RaMe$_2$Bu**	Sc(OTf)$_3$	Imidazole	67	91
12[d]	**L-RaMe$_2$Bu**	Sc(OTf)$_3$	Imidazole	90	91

[a] Unless otherwise noted, the reactions were performed with metal/ligand (1 : 1, 10 mol%), **1a** (0.10 mmol), **2a** (0.10 mmol) and additive (0.10 eq.) in THF (1.0 mL) at 35 °C for 72 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The reaction was performed with **1a** (0.12 mmol), metal–ligand (1 : 1.05, 10 mol%), **2a** (0.10 mmol) and additive (0.15 eq.) in THF (1.0 mL) at 35 °C for 72 h. The dr were all over 19 : 1 detected by ^{1}H NMR spectra. PMP = *p*-methoxyphenyl, Bn = benzyl.

[a] *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, P. R. China. E-mail: xmfeng@scu.edu.cn; Fax: +86 28 85418249; Tel: +86 28 85418249*

[b] *Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), P. R. China*

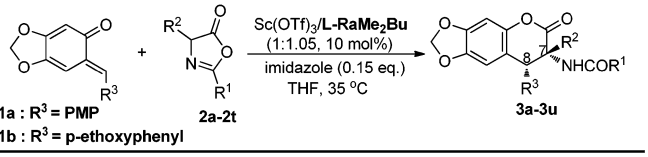
† Electronic supplementary information (ESI) available: Additional experimental and spectroscopic data. CCDC 1039793. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc10343b

THF. Various metal salts complexing with chiral L-proline-derived *N*,*N*′-dioxide **L-PrMe$_2$** were investigated (Table 1, entries 1–3). The target product **3a** was obtained in 60% yield with only 19% ee when Ni(OTf)$_2$ was applied as the metal (Table 1, entry 1), meanwhile, the Michael addition product was isolated unexpectedly. However, when other metals were employed in the reaction, the Michael addition product was not detected. The complex of Yb(OTf)$_3$ also gave a moderate result (Table 1, entry 2). Inspiringly, Sc(OTf)$_3$ was able to improve the ee to 74% sharply albeit with a decreased yield (Table 1, entry 3). Subsequently, various ligands were evaluated (Table 1, entries 4–7). It was found that the steric hindrance at the amide moiety of the *N*,*N*′-dioxide ligands affected the enantioselectivity of the reaction apparently. Upon improving the steric hindrance from the 2,6-dimethyl to 2,6-diisopropyl group, the ee was decreased sharply from 74% to 25% (Table 1, entries 3 and 4). **L-PrMe$_2$Bu** with an additional tertiary butyl substitution on the *para*-position of the phenyl ring compared to **L-PrMe$_2$** increased the ee to 80%, however, decreased the yield to less than 5% (Table 1, entry 5). L-Pipecolic acid derived **L-PiMe$_2$Bu** and L-ramipril derived ligand **L-RaMe$_2$Bu** could improve the yield a little, and the latter could also give 80% ee. In order to improve the reactivity of the reaction, basic additives were designedly added in the catalytic system to facilitate the enolization of azlactones. As expected, both inorganic and organic bases improved the reactivity (Table 1, entries 8–12), and the latter were more beneficial for the enantioselectivity. Imidazole as the additive could not only increase the yield to 67% but also promote the ee to 91%. Finally, by adjusting the metal to ligand ratio to 1 : 1.05 and the proportion of **1a** to **2a** to 1.2 : 1.0, 3,4-dihydrocoumarin **3a** was obtained in 90% yield with 91% ee (Table 1, entry 12). In all cases, the diastereoselectivity of the reaction was over 19 : 1.

Under the optimized reaction conditions (Table 1, entry 12), a wide range of azlactones **2** were investigated. As shown in Table 2, azlactones with either electron-withdrawing or electron-donating substituents on the phenyl ring in the R^1 group could be smoothly converted to the corresponding products in high yields, good enantioselectivities and excellent diastereoselectivities (up to 94% yield, 96% ee, >19 : 1 dr) (Table 2, entries 1–14). In addition, azlactone **2o** with two benzyl groups was well tolerated in the reaction, giving 63% yield and 94% ee (Table 2, entry 15). When substituent R^2 was examined, both benzyl and alkyl groups were compatible. Substituents on the benzyl group exhibited an obvious electronic effect. The yield increased correspondingly with the electron-withdrawing decreased (Table 2, entries 16–18). For alkyl substituted **2s** and **2t**, high ee values (82% ee, 77% ee) and moderate yields (75% yield, 71% yield) were obtained (Table 2, entries 19 and 20). Moreover, the reaction proceeded well with substrate **1b**, which contained a slightly steric hindrance change (Table 2, entry 21). The absolute configuration of product **3d** was determined to be (7*R*,8*R*) by X-ray crystallography analysis, the others were confirmed in comparison with the Cotton effect in the CD spectra (see the ESI† for details).

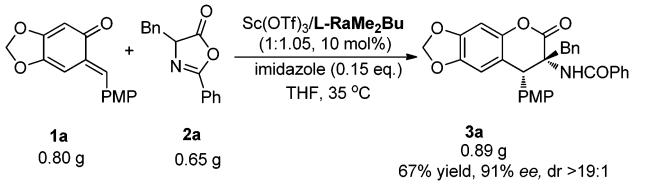
Considering the potential biological activities of dihydrocoumarins and in order to show the synthetic utility of the catalyst system, the gram-scale synthesis of **3a** was performed. Under the optimized reaction conditions, 3.12 mmol (0.80 g) QM **1a** and 2.60 mmol (0.65 g) azlactone **2a** reacted well to afford the desired adduct **3a** in 67% yield (0.89 g) with 91% ee and >19 : 1 dr (Scheme 1).

Table 2 Substrate scope of the asymmetric IEDDA reaction



Entry[a]	R^1	R^2	Yield[b] (%)	ee[c,f] (%)
1	Ph	Bn	90 (**3a**)	91$_{(7R,8R)}$
2	4-FC$_6$H$_4$	Bn	84 (**3b**)	92$_{(7R,8R)}$
3	4-ClC$_6$H$_4$	Bn	89 (**3c**)	94$_{(7R,8R)}$
4	4-BrC$_6$H$_4$	Bn	90 (**3d**)	91$_{(7R,8R)}$
5	4-NCC$_6$H$_4$	Bn	64 (**3e**)	94$_{(7R,8R)}$
6	4-F$_3$CC$_6$H$_4$	Bn	68 (**3f**)	92$_{(7R,8R)}$
7	4-MeC$_6$H$_4$	Bn	90 (**3g**)	93$_{(7R,8R)}$
8	4-EtC$_6$H$_4$	Bn	87 (**3h**)	92$_{(7R,8R)}$
9	4-MeOC$_6$H$_4$	Bn	85 (**3i**)	90$_{(7R,8R)}$
10	4-O$_2$NC$_6$H$_4$	Bn	94 (**3j**)	96
11	3-ClC$_6$H$_4$	Bn	88 (**3k**)	91$_{(7R,8R)}$
12	2-ClC$_6$H$_4$	Bn	85 (**3l**)	91
13[d]	3,5-Me$_2$C$_6$H$_3$	Bn	80 (**3m**)	92$_{(7R,8R)}$
14	3,5-(O$_2$N)$_2$C$_6$H$_3$	Bn	94 (**3n**)	93
15	Bn	Bn	63 (**3o**)	94$_{(7R,8R)}$
16	Ph	4-FC$_6$H$_4$CH$_2$	42 (**3p**)	91$_{(7R,8R)}$
17	Ph	4-ClC$_6$H$_4$CH$_2$	70 (**3q**)	92$_{(7R,8R)}$
18	Ph	4-BrC$_6$H$_4$CH$_2$	91 (**3r**)	91$_{(7R,8R)}$[f]
19	Ph	CH$_3$SCH$_2$CH$_2$	75 (**3s**)	82$_{(7R,8R)}$
20	Ph	Me	71 (**3t**)	77$_{(7R,8R)}$
21[e]	Ph	H	70 (**3u**)	91$_{(7R,8R)}$

[a] Unless otherwise noted, the reactions were performed with **L-RaMe$_2$Bu**-Sc(OTf)$_3$ (1 : 1.05, 10 mol%), **1a** (0.12 mmol), **2** (0.1 mmol) and imidazole (0.15 eq.) in THF (1.0 mL) at 35 °C for 72 h. [b] Isolated yield. [c] Determined by HPLC analysis. [d] The reaction was performed with imidazole (0.3 eq.) at 35 °C for 96 h. [e] In the reaction **1a** was changed to **1b**. [f] The absolute configuration of **3d** was determined to be (7*R*,8*R*) by X-ray crystallographic analysis, others were confirmed by comparison with the CD spectra. The dr were all over 19 : 1 detected by ^{1}H NMR spectra.



Scheme 1 The gram-scale synthesis of **3a**.

In order to investigate the reaction pathway, the Operando IR and control experiments were carried out (Fig. 1). In the Operando IR experiments, it was clearly demonstrated that the amount of product **3a** increased with the consumption of QM **1a** and azlactone **2a**. Additionally, the signal of the Michael-addition product **3aa** was not detected. On the other hand, when **3aa** was exposed to the standard reaction system, no dihydrocoumarin **3a** was obtained. All the experiments indicate that the reaction undergoes the concerted pathway rather than the stepwise pathway.

On the basis of the experimental results, our previous work[8] and the absolute configuration of the products, a possible transition-state model was proposed. As shown in Fig. 2, the tetradentate *N*,*N*′-dioxide **L-RaMe$_2$Bu** and monodentate QM[9,10] **1a** coordinate to

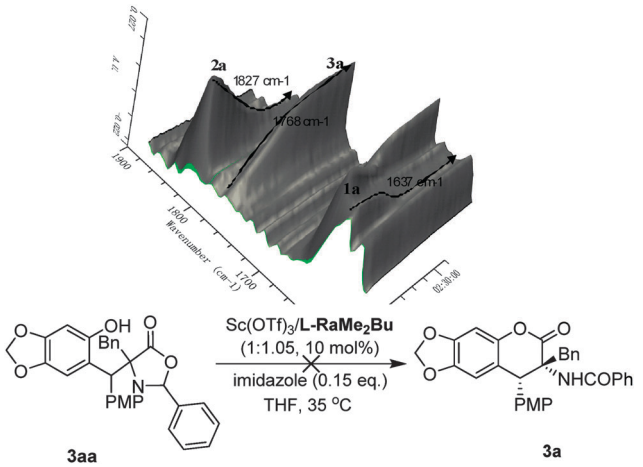


Fig. 1 The Operando IR and control experiments.

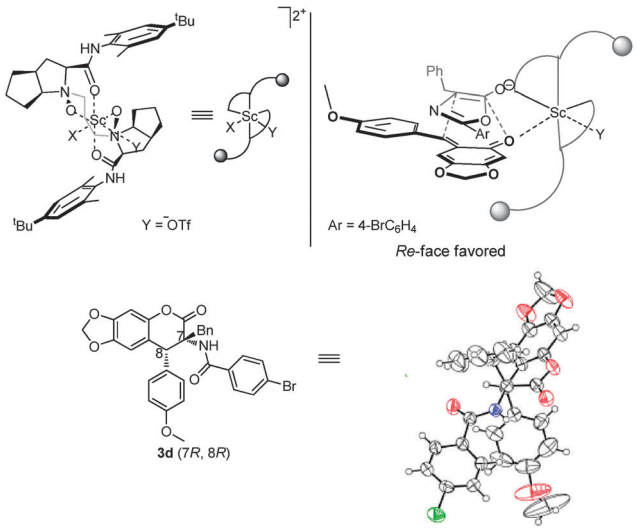


Fig. 2 Proposed transition state and the absolute configuration of **3d**.

scandium(III) to form a rigid octahedral complex. The group underneath the ligand shields the *Si* face of the QM. Therefore, azlactone **2d** attacks predominantly from the *Re* face to give the product **3d** in an exclusively *endo* fashion and with a (7*R*,8*R*)-configuration.[11]

In conclusion, we have developed an efficient method for the asymmetric synthesis of dihydrocoumarins with nitrogen atom substituents in high yields with excellent enantioselectivities and diastereoselectivities firstly by using the inverse-electron-demand hetero-Diels–Alder reaction of QMs and azlactones. Operational simplicity and mild reaction conditions were attributed to the efficiency of the chiral *N*,*N*′-dioxide–Sc(III) complex. Further application of these kinds of catalysts to other reactions is underway.

We appreciate the National Basic Research Program of China (973 Program: No. 2011CB808600) and the National Natural Science Foundation of China (No. 21372162, 21290182, and 21172151) for financial support.

Notes and references

1 (*a*) R. D. H. Murray, J. Mendez and S. A. Brown, *The Natural Coumarin: Occurrence, Chemistry, and Biochemistry*, Wiley, New York, 1982; (*b*) R. O'Kennedy and R. D. Thornes, *Coumarins: Biology, Applications, and Mode of Action*, Wiley, Chichester, UK, 1st edn, 1997; (*c*) C. A. Kontogiorgis and D. J. Hadjipavlou-Litina, *J. Med. Chem.*, 2005, **48**, 6400.

2 (*a*) Y. L. Kuang, X. H. Liu, L. Chang, M. Wang, L. L. Lin and X. M. Feng, *Org. Lett.*, 2011, **13**, 3814; (*b*) P. Niharika, B. V. Ramulu and G. Satyanarayana, *Org. Biomol. Chem.*, 2014, **12**, 4347; (*c*) J. L. Li, S. L. Zhou, B. Han, L. Wu and Y. C. Chen, *Chem. Commun.*, 2010, **46**, 2665; (*d*) M. Marchetti, O. Piccolo and F. Ulgheri, *J. Org. Chem.*, 2007, **72**, 6056; (*e*) S. Aoki, K. Yamamoto, J. Yamada and T. Kitamura, *Tetrahedron*, 2005, **61**, 9291; (*f*) M. A. Mcguire, S. C. Shilcrat and E. Sorenson, *Tetrahedron Letters*, 1999, **40**, 3293; (*g*) O. D. Engl, S. P. Fritz, A. Käslin and H. Wennemers, *Org. Lett.*, 2014, **16**, 5454; (*h*) D. F. Lu, Y. J. Li and Y. F. Gong, *J. Org. Chem.*, 2010, **75**, 6900; (*i*) C. B. Jacobsen, Ł. Albrecht, J. Udmark and K. A. Jørgensen, *Org. Lett.*, 2012, **14**, 5526; (*j*) J. Barluenga, F. Andina and F. Aznar, *Org. Lett.*, 2006, **8**, 2703; (*k*) B. C. Hong, P. Kotame and G. H. Lee, *Org. Lett.*, 2011, **13**, 5758; (*l*) X. H. Li, P. Fang, D. Chen and X. L. Hou, *Org. Chem. Front.*, 2014, **1**, 969.

3 E. Alden-Danforth, M. T. Scerba and T. Lectka, *Org. Lett.*, 2008, **10**, 4951.

4 H. Lv, L. You and S. Ye, *Adv. Synth. Catal.*, 2009, **351**, 2822.

5 For the cycloaddition reactions of azlactones, see: (*a*) S. X. Dong, X. H. Liu, Y. Zhu, P. He, L. L. Lin and X. M. Feng, *J. Am. Chem. Soc.*, 2013, **135**, 10026; (*b*) W. S. Sun, G. M. Zhu, C. Y. Wu, G. F. Li, L. Hong and R. Wang, *Angew. Chem. Int. Ed.*, 2013, **52**, 8633; (*c*) X. X. Jiang, H. Zhu, X. M. Shi, Y. Zhong, Y. F. Li and R. Wang, *Adv. Synth. Catal.*, 2013, **355**, 308; (*d*) F. Esteban, R. Alfaro, F. Yuste, A. Parra, J. L. J. Ruano and J. Alemán, *Eur. J. Org. Chem.*, 2014, 1395.

6 For examples of inverse-electron-demand hetero-Diels–Alder reactions, see: (*a*) K. Gademann, D. E. Chavez and E. N. Jacobsen, *Angew. Chem.*, 2002, **114**, 3185; (*b*) Ł. Albrecht, G. Dickmeiss, C. F. Weise, C. Rodrguez-Escrich and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2012, **51**, 13109; (*c*) C. J. Abraham, D. H. Paull, M. T. Scerba, J. W. Grebinski and T. Lectka, *J. Am. Chem. Soc.*, 2006, **128**, 13370; (*d*) R. A. A. Foster and M. C. Willis, *Chem. Soc. Rev.*, 2013, **42**, 63; (*e*) A. C. Knall and C. Slugovc, *Chem. Soc. Rev.*, 2013, **42**, 5131; (*f*) X. X. Jiang and R. Wang, *Chem. Rev.*, 2013, **113**, 5515.

7 (*a*) D. F. Reinhold, N. J. North Plainfield, J. H. Markillie, K. Mich and M. Sletzinger, *US Pat.*, 3161655, 1964; (*b*) J. G. Rico, *Tetrahedron Letter*, 1994, **35**, 6599; (*c*) D. Cabaret, S. A. Adediran, M. J. Garcia Gonzalez, R. F. Pratt and M. Wakselman, *J. Org. Chem.*, 1999, **64**, 713; (*d*) P. R. Bovy, M. Miyano, J. G. Rico and T. E. Rogers, *PCT Int. Appl.*, 9312103, 1993; (*e*) S. X. Dong, X. H. Liu, Y. L. Zhang, L. L. Lin and X. M. Feng, *Org. Lett.*, 2011, **13**, 5060.

8 For selected examples using chiral *N*,*N*′-dioxide ligands, see: (*a*) X. H. Liu, L. L. Lin and X. M. Feng, *Acc. Chem. Res.*, 2011, **44**, 574; (*b*) A. Hassner and I. Namboothiri, *Organic Syntheses Based on Name Reactions*, Elsevier, Oxford, 3th edn, 2011, p. 408; (*c*) X. M. Feng and X. H. Liu, *Scandium Compounds, Productions and Applications*, ed. V. A. Greene, Nova Science, New York, 2011, pp. 1–48; (*d*) K. Zheng, L. L. Lin and X. M. Feng, *Acta Chim. Sinica.*, 2012, **70**, 1785; (*e*) J. Ji, L. L. Lin, Y. H. Zhang, Y. B. Liu, X. H. Liu and X. M. Feng, *Adv. Synth. Catal.*, 2013, **355**, 2764; (*f*) X. H. Liu, L. L. Lin and X. M. Feng, *Org. Chem. Front.*, 2014, **1**, 298; (*g*) M. S. Xie, X. X. Wu, G. Wang, L. L. Lin and X. M. Feng, *Acta Chim. Sinica.*, 2014, **72**, 856.

9 L. Jurd, *Tetrahedron*, 1977, **33**, 163.

10 For the selected examples of QMs, see: (*a*) *Quinone Methides*, ed. S. E. Rokita, Wiley, New York, 2009; (*b*) D. L. Boger and S. M. Weinreb, *Hetero Diels–Alder Methodology in Organic Synthesis*, Academic Press, San Diego, 1987; (*c*) Y. Luan and S. E. Schaus, *J. Am. Chem. Soc.*, 2012, **134**, 19965; (*d*) H. Lv, W. Q. Jia, L. H. Sun and S. Ye, *Angew. Chem. Int. Ed.*, 2013, **52**, 8607.

11 CCDC 1039793 (**3d**) for more data see ESI†.