Tetrahedron Letters 51 (2010) 3836–3839

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Iron-catalyzed Michael reactions revisited: a synthetically useful process for the preparation of tri-carbonyl compounds and chiral warfarin

Hua-Meng Yang [a], Yue-Hua Gao [b], Li Li [a], Zhen-Yu Jiang [a], Guo-Qiao Lai [a,*], Chun-Gu Xia [b], Li-Wen Xu [a,b,*]

[a] Key Laboratory of Organosilicon Chemistry and Material Technology of Ministry of Education, Hangzhou Normal University, Hangzhou 310012, PR China
[b] State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, PR China

ARTICLE INFO

Article history:
Received 19 March 2010
Revised 14 May 2010
Accepted 18 May 2010
Available online 24 May 2010

Keywords:
Iron catalysis
Michael reaction
Warfarin
Asymmetric catalysis
Primary amine

ABSTRACT

The LBAs (Lewis acid-assisted Brønsted acid catalysis) is proposed as possible mechanistic process in the simple $FeCl_3$-catalyzed Michael reactions of chalcones with active methylene compounds in organic solvents. And iron salts were found to be effective promoters in the asymmetric Michael addition of 4-hydroxycoumarin to α,β-unsaturated ketone, which resulted in excellent yield and high level of enantioselectivity (up to 91% ee) in the presence of low catalytic amount of iron and simple chiral primary amine.

The Michael reaction of appropriate carboanionic reagents to α,β-unsaturated carbonyl compounds is the most direct approach for the preparation of polysubstituted tri-carbonyl compounds, which also is an efficient method for carbon–carbon bond formation and has extensive applications to remote functionalization in organic synthesis.[1] In the past decades, the reaction has been traditionally performed using various basic catalysts or reagents, such as NaOH,[2] $Ba(OH)_2$,[3] and Mg-Al-*O*-*t*-Bu hydrotalcite.[4] However, there are some disadvantages under the strong basic conditions. For example, in the presence of strong bases, side reactions, such as aldol or self-aldol addition, polymerizations, retrogressions, and rearrangements, are frequently encountered. Recently, various Michael reactions promoted by organic base/acid catalysts or under microwave irradiation have been developed to avoid the usual drawbacks of the basic process.[5] Among the various metal salts used to catalyze this Michael reaction, iron salts, such as iron(III) chloride hexahydrate ($FeCl_3{\cdot}6H_2O$), were clearly the catalysts of choice for the Michael reaction of alkyl enones with β-keto esters.[6] Interestingly, in their report,[6a] the $FeCl_3{\cdot}6H_2O$ showed poor catalytic activity at room temperature in organic media.

In most cases, iron and its compounds are low-toxic and environmentally friendly, therefore, it has been attracted much attention in a great deal of useful organic transformations in recent years.[7] Since 1982,[8] the iron-catalyzed Michael reaction has been well documented and successfully used in the synthesis of multicarbonyl compounds from aliphatic enones or nitroolefins and dicarbonyl compounds under solvent-free conditions.[6] While the mechanistic proposal of one-center template reaction is in accordance with experimental observations, ESI, and DFT calculations,[9] more information and evidence are desired to supplement or understand the mechanism of Michael reaction. In addition, despite the potential of iron salts as privileged catalysts in organic synthesis being realized, the development of highly enantioselective iron-catalyzed organic transformation is highly desired.[10]

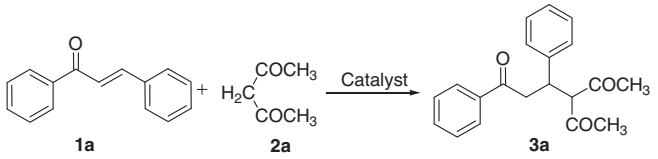
Herein, we focused on the iron-catalyzed Michael reactions by using chalcones and active methylene as model substrates to evaluate the possible mechanistic process of LBAs (Lewis acid-assisted Brønsted acid catalysis). Another aim of the present work is to establish a novel and efficient LBAs-based chiral catalyst system for asymmetric Michael reaction of 4-hydroxycoumarin to *trans*-4-phenyl-3-buten-2-one to make chiral warfarin.

To investigate the solvent effect and catalytic efficiency of different iron salts in organic media, the Michael addition of active methylenes to aromatic chalcones was considered as the ideal model reaction. Initially, we carried out the optimization of a variety of reaction conditions, employing different iron salts for the model Michael reaction of chalcone and acetylacetone. As shown in Table 1, acceptable yield (39–79%) of the desired product was obtained with $FeCl_3{\cdot}6H_2O$ or $Fe(ClO_4)_3{\cdot}xH_2O$ as catalyst in toluene at room temperature after 12 h (entries 1 and 2), however, the Michael reaction did not proceed at all with several iron salts, such as $FeSO_4{\cdot}7H_2O$, $FeCl_2{\cdot}4H_2O$, $Fe(NO_3)_3{\cdot}9H_2O$, and $Fe(OAc)_2$ (entries

* Corresponding authors. Tel.: +86 0571 28867756; fax: +86 0571 28865135 (L.-W.X.).
E-mail addresses: licpxulw@yahoo.com, liwenxu@hznu.edu.cn (L.-W. Xu).

0040-4039/$ - see front matter Crown Copyright © 2010 Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.05.074

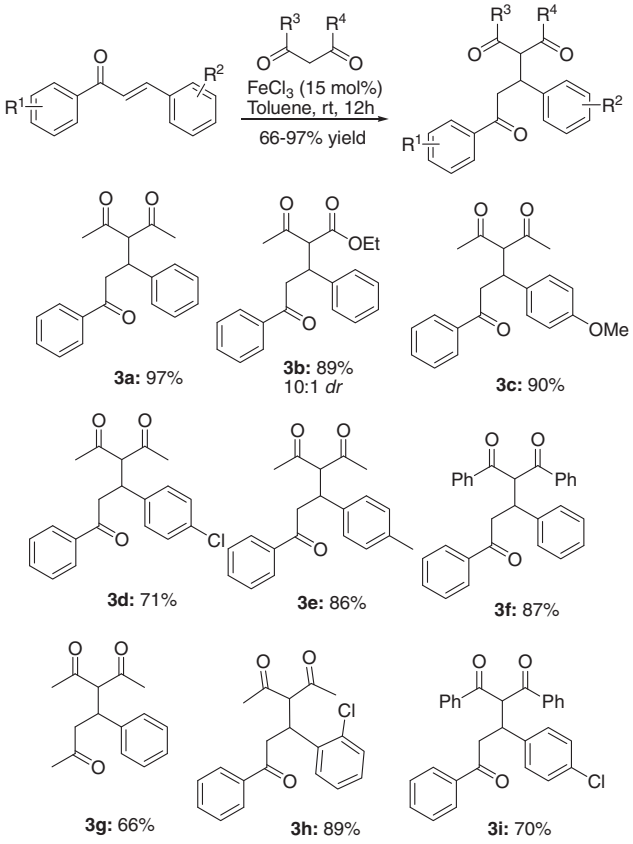
Table 1
Michael addition reaction of acetylacetone with chalcone promoted by different metal salt



1a 2a 3a

Entry[a]	Metal salt	Solvent	Yield[b] (%)
1	$FeCl_3·6H_2O$	Toluene	39
2	$Fe(ClO_4)_3·xH_2O$	Toluene	79
3	$FeCl_2·4H_2O$	Toluene	NR[c]
4	$Fe(NO_3)_3·9H_2O$	Toluene	NR[c]
5	$Fe(OAc)_2$	Toluene	NR[c]
6	$FeSO_4·7H_2O$	Toluene	NR[c]
7	$FeBr_3$	Toluene	91
8	$FeCl_3$	Toluene	97
9	$FeCl_3$	CH_2Cl_2	88
10[d]	$FeCl_3$	THF	10
11[e]	$FeCl_3$	CH_3OH	7
12[f]	$FeCl_3$	Ethanol	Trace
13	$Fe(acac)_3$	Toluene	NR[c]
14	HCl	Toluene	20[g]
15	$Fe(acac)_3$ + HCl	Toluene	>95
16	$Fe(acac)_3$ + TsOH	Toluene	>95

[a] Reaction conditions: 15 mol % of metal salt, 1.5 mmol/1.0 mmol, of acetylacetone/chalcone; and 1.5 mL of solvent at room temperature for 12 h unless otherwise noted.
[b] Isolated yields.
[c] No reaction.
[d] 24 h.
[e] 48 h.
[f] 70 h.
[g] There are many by-products in this reaction.

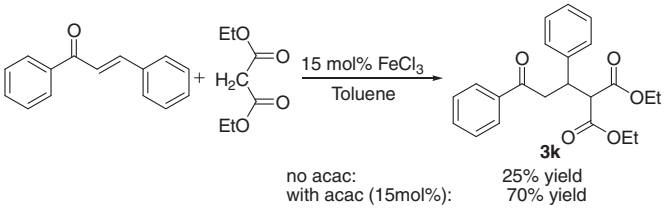


Scheme 1. $FeCl_3$-catalyzed Michael reactions of active methylene compounds with chalcones: 15 mol % of $FeCl_3$, 1.5 mmol/1.0 mmol, of active methylene compounds/chalcones; and 1.5 mL of toluene at room temperature for 12 h.

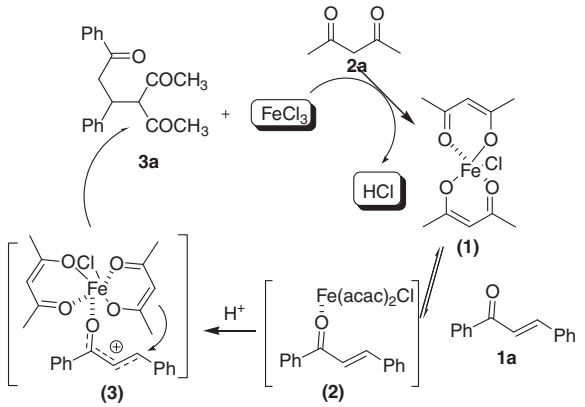
3–6), which showed the anion of iron salt has a pronounced effect in activation of carbonyl substrates. We then carried out the reaction in the presence of anhydrous $FeCl_3$ and $FeBr_3$ in toluene at room temperature, the reaction is clean and the yield was increased to higher level (entries 7 and 8: 97% and 91%, respectively). The screening of the solvent revealed that poor results were displayed in other solvents, such as THF and CH_3OH (entries 10 and 11), and the reaction did not proceed at all when using ethanol as the solvent (entry 12). Very interestingly, the reaction performed with $Fe(acac)_3$ failed in providing the desired Michael adduct. The observed acceleration of the iron-mediated Michael addition showed that the anion of iron salt played a crucial role when counterion was changed from acetate to chloride.

We then investigated the reaction scope of this catalytic system and its tolerance of functional groups in the case of other chalcones **1** and active methylene compounds **2**. As shown in Scheme 1, the optimized reaction conditions were applicable to various substrates. Whether using aromatic or aliphatic diketones, iron efficiently promoted the reaction with good to excellent yields. Ethyl acetoacetate was also found to be a suitable substrate. Unfortunately, the reaction of diethyl malonate with chalcone afforded the desired product in only 25% yield with trace byproduct. On the basis of previous results, we felt that the use of an appropriate additive to form iron enolate of dimethyl malonate would allow us to realize a mild and general procedure for the synthesis of **3k**. As we expected, using acetylacetone as an additive in the Michael reaction of dimethyl malonate with chalcone, the reaction was proceeded successfully with good yield (70% isolated yield). To the best of our knowledge, this is the first example of the iron-catalyzed Michael reactions of chalcones and unactive malonate compounds promoted by acetylacetone, which maybe due to the activation of iron enolate (Scheme 2). In this case, the replacement of $FeCl_3$/acac system with $Fe(acac)_3$/HCl resulted in low yield (10%), which is due to low nucleophilic activity of ethyl malonate.

The mechanism of iron-catalyzed Michael reaction of 1,3-dicarbonyl compounds has been reported by Christoffers and co-workers, in which a one-center template mode was established.[9] It is reasonable that $Fe(acac)_3$ is significantly less active than the $FeCl_3·6H_2O$ or $FeCl_3$ because it does not readily offer a vacant coordination site for the enone. However, it is difficult to explain why anhydrous $FeCl_3$ is significantly more active than $FeCl_3·6H_2O$ in toluene. In addition, $Fe(acac)_3$ is also an excellent catalyst in the presence of catalytic amount of brønsted acid, such as TsOH and HCl. Based on our experimental results and macroscopic opinion, a suggested and more practical mechanism with Lewis acid-assisted Brønsted acid catalysis (LBA)[11] is proposed in Scheme 3. The reasons for this proposal of LBA are as follows: (a) The $Fe(acac)_3$-catalyzed Michael addition reactions of acetylacetone with chalcone gave no desired product, indicating that the Michael addition proceeded with Brønsted acidic HCl as catalyst. (b) Without the iron catalyst, the reaction proceeded with low yield and poor chemoselectivity. Many products of side reactions with mixtures formed in the presence of only HCl. Therefore, the major role of the iron



Scheme 2. $FeCl_3$-catalyzed Michael reaction of diethyl malonate with chalcone.



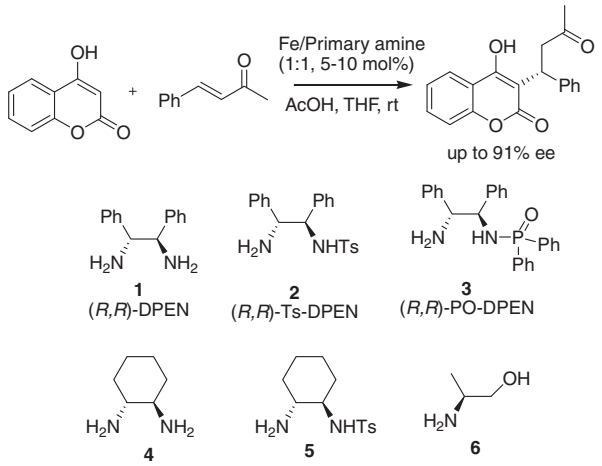
Scheme 3. Proposed LBAs mechanism for the $FeCl_3$-catalyzed Michael addition reactions.

catalyst lied in the formation of iron–dicarbonyl complex for the improvement of selectivity. (c) When a catalytic amount of HCl or TsOH was used in the $Fe(acac)_3$-catalyzed Michael addition reactions of acetylacetone with chalcone, the desired products were also formed with excellent chemoselectivity and yields (up to 97%), which supported the proposed mechanism of Lewis acid-assisted Brønsted acid catalysis (LBA).

Encouraged by previous findings, we turned our attention to the Michael addition of a β-keto ester analogue, 4-hydroxycoumarin, to *trans*-4-phenyl-3-buten-2-one (benzylideneacetone) for the synthesis of warfarin. Wafarin is a Vitamin K antagonist, and both racemic and chiral wafarin have been introduced for clinical use as the most widely prescribed anticoagulant drug in North American.[12] In addition, the syntheses of chiral warfarin were traditionally performed via auxiliary strategy,[13] asymmetric hydrogenation,[14] and hetero-Diels–Alder addition[15], and recently by organocatalytic Michael addition of 4-hydroxycoumarin to *trans*-4-phenyl-3-buten-2-one.[16]

We then investigated the asymmetric $FeCl_3$-catalyzed Michael addition of 4-hydroxycoumarin to *trans*-4-phenyl-3-buten-2-one. In an initial screening, we evaluated several simple and commercial available chiral amines, especially primary amino derivatives, for their ability to coordinate with iron and promote the Michael addition through possible enamine intermediate of 4-hydroxycoumarin. As representative chiral amines, primary amines **1**–**6** are listed here and they exhibited different levels of enantio-induction. As shown in Table 2, we found that Ts-DPEN (**2**)[17] could promote the Michael addition of 4-hydroxycoumarin to *trans*-4-phenyl-3-buten-2-one in the absence of acetic acid and $FeCl_3$ (entry 2), however, the yield is low and enantioselectivity is moderate (64% ee). To our delight, the addition of $FeCl_3$ could improve the yield, and we found that the decrease of catalytic amount of iron and primary amine to 5 mol % acceptable yield and higher enantioselectivity (81% ee) was achieved in this reaction (entry 3). The synergistic effect of iron salt and primary amine is pronounced, which proved that the concept of combining transition metal catalysis and organocatalysis is a promising strategy to improve the enantioselectvity.[18] We then screened different primary amines for the iron/primary amine-mediated Michael reaction of 4-hydroxycoumarin with *trans*-4-phenyl-3-buten-2-one, only unmodified DPEN (**1**) reserved the enantioselectivity and other primary amines resulted in poor yields and enantioselectivities (entries 4–8 and 16). We explored the iron salts with different anions for this Michael reaction, and the results are summarized in entries 9–12 of Table 2. $FeCl_2{\cdot}4H_2O$, $Fe(ClO_4)_3$, and $FeCl_3$ gave good enantioselectivities, which prompted us to continue investigate the effect of AcOH. When the amount of AcOH was increased to 10 equiv, all the three iron salts evaluated gave good yields and excellent enantioselectivity (90–91% ee) in the presence of primary amine **1** or **3**, even with the analog of Ts-DPEN, PO-DPEN (**3**).[19]

Table 2
Effect of iron and primary amines on warfarin synthesis[a]



Entry	FeX_n	Amine	Fe/amine (mol %)	Yield[b] (%)	ee[c] (%)
1	—	**2**	10	47	64
2	—	**2**	10	20	64[d]
3	$FeCl_3$	**2**	5	60	81
4	$FeCl_3$	**1**	5	64	83
5	$FeCl_3$	**3**	5	37	75
6	$FeCl_3$	**4**	5	30	40
7	$FeCl_3$	**5**	5	NR[e]	—
8	$FeCl_3$	**6**	5	NR[e]	—
9	$Fe(ClO_4)_3$	**1**	5	28	73
10	$Fe(acac)_3$	**1**	5	39	53
11	$FeSO_4{\cdot}7H_2O$	**1**	5	41	68
12	$FeCl_2{\cdot}4H_2O$	**1**	5	87	83
13	$FeCl_3$	**3**	5	80	90
14	$Fe(ClO_4)_3$	**1**	10	50	91
15	$FeCl_2{\cdot}4H_2O$	**1**	10	90	90
16	—	**1**	5	47	84

[a] Experimental conditions: a mixture of iron salt and primary amine (1:1, 5–10 mol %), 4-hydroxycoumarin (1 mmol), *trans*-4-phenyl-3-buten-2-one (1.5 mmol), AcOH (entries 1–12 except entry 3: 2 equiv, entries 13–16: 10 equiv AcOH), and THF (2 mL), at room temperature for 24 h.
[b] Isolated yield.
[c] Determined by HPLC using a chiral Daicel AD-H column.
[d] No addition of AcOH.
[e] No reaction.

In summary, iron-catalyzed Michael reaction of chalcone with active methylene compounds works smoothly in organic media, which has the advantages of mild reaction conditions, convenient operation, high atom efficiency, and structural diversity of the desired products. Further investigations of asymmetric iron-catalyzed Michael addition of 4-hydroxycoumarin to *trans*-4-phenyl-3-buten-2-one provided a new synthetically useful method for the preparation of chiral warfarin with excellent enantioselectivity (up to 91% ee). Present studies are directed toward the improvement of enantioselectivity of the reaction by the cooperation of metal catalysis and organocatalysis.

Acknowledgments

This work was supported by the National Natural Science Founder of China (No. 20973051) and Zhejiang Provincial Natural Science Foundation of China (Y4090139).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.074.

References and notes

1. Mekonnen, A.; Carlson, R. *Eur. J.Org. Chem.* **2006**, 2005.
2. Rehberg, V. R.; Kröhnke, F. *Liebigs Ann. Chem.* **1968**, *717*, 91.
3. García-Raso, A.; García-Raso, J.; Campaner, B.; Mestres, R.; Sinisterra, J. V. *Synthesis* **1982**, 1037.
4. Choudary, B. M.; Kantam, M. L.; Kavita, B.; Reddy, C. V.; Figueras, F. *Tetrahedron* **2000**, *56*, 9357.
5. (a) Wang, J.; Li, H.; Zu, L. S.; Jiang, W.; Xie, H. X.; Duan, W. H.; Wang, W. *J. Am. Chem. Soc.* **2006**, *128*, 12652; (b) Shankar, R.; Jha, A. K.; Singh, U. S.; Hajela, K. *Tetrahedron Lett.* **2006**, *47*, 3077; (c) Li, J. T.; Chen, G. F.; Cheng, Z. L.; Li, T. S. *Synth. Commun.* **2003**, *33*, 353; (d) Saidi, M. R.; Azizi, N.; Akbari, E.; Ebrahimi, F. *J. Mol. Catal. A: Chem.* **2008**, *292*, 44; (e) Reddy, C.; Reddy, V.; Verkade, J. G. *J. Org. Chem.* **2007**, *72*, 3093; (f) Veldurthy, B.; Clacens, J. M.; Figueras, F. *Adv. Synth. Catal.* **2005**, *347*, 767.
6. (a) Christoffers, J. *Chem. Commun.* **1997**, 943; (b) Christoffers, J.; Oertling, H. *Tetrahedron* **2000**, *56*, 1339; (c) Christoffers, Y. *Synlett* **2001**, 723.
7. (a) Bolm, C.; Legros, J.; Paih, J. L.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217; (b) Correa, A.; Mancheño, O. G.; Bolm, C. *Chem. Soc. Rev.* **2008**, *37*, 1108. and references cited therein; (c) Enthaler, S.; Junge, K.; Beller, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3317; (d) Yadav, J. S.; Reddy, B. V. S.; Narasimhulu, G.; Purnima, K. V. *Tetrahedron Lett.* **2009**, *50*, 5783; (e) Maeda, S.; Obora, Y.; Ishi, Y. *Eur. J. Org. Chem.* **2009**, 4067; (f) Mukherjee, A.; Pati, K.; Liu, R. S. *J. Org. Chem.* **2009**, *74*, 6311; (g) Fan, J. M.; Gao, L. F.; Wang, Z. Y. *Chem. Commun.* **2009**, 5021.
8. Fei, C. P.; Chan, T. H. *Synthesis* **1982**, 467.
9. (a) Pelzer, S.; Kauf, T.; Van Wüllen, C.; Christoffers, J. *J. Organomet. Chem.* **2003**, *684*, 308; (b) Trage, C.; Schröder, D.; Schwarz, H. *Chem. Eur. J.* **2005**, *11*, 619; (c) Asthalter, T.; Rajagopalan, S.; Kauf, Th.; Rabe, V.; Christoffers, J. *J. Phys. Chem. A* **2008**, *112*, 11514; (d) Bauer, M.; Kauf, T.; Christoffers, J.; Bertagnolli, H. *Phys. Chem. Chem. Phys.* **2005**, *7*, 2664.
10. Selected examples, see: (a) Costas, M.; Tipton, A. K.; Chen, K.; Jo, D. H.; Que, L., Jr. *J. Am. Chem. Soc.* **2001**, *123*, 6722; (b) Legros, J.; Bolm, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5487; (c) Legros, J.; Bolm, C. *Chem. Eur. J.* **2005**, *11*, 1086; (d) Gelalcha, F. G.; Bitterlich, B.; Anikumar, G.; Tse, M. K.; Beller, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 7293; (e) Egami, H.; Katsuki, T. *J. Am. Chem. Soc.* **2009**, *131*, 6082; (f) Suzuki, K.; Oldenburg, P. D.; Que, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1887; (g) Morris, R. H. *Chem. Soc. Rev.* **2009**, *38*, 2282.
11. (a) Ishihara, K.; Ishida, Y.; Nakamura, S.; Yamamoto, H. *Synlett* **1997**, 758; (b) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924; (c) Yamamoto, H. *Tetrahedron* **2007**, *35*, 8377; (d) Rauniyar, V.; Zhai, H. M.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481; (e) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744.
12. Holbrook, A. M.; Pereira, J. A.; Labiris, R.; McDonald, H.; Douketis, J. D.; Crowther, M.; Wells, P. S. *Arch. Intern. Med.* **2005**, *165*, 1095.
13. Demir, A. S.; Tanyeli, C.; Gülbeyaz, V.; Akgün, H. *Turk. J. Chem.* **1996**, *20*, 139–145.
14. (a) Robinson, A.; Li, H. Y.; Feaster, J. *Tetrahedron Lett.* **1996**, *37*, 8321; (b) Tsuchiya, Y.; Hamashima, Y.; Sodeoka, M. *Org. Lett.* **2006**, *8*, 4851.
15. Cravotto, G.; Nano, G. M.; Palmisano, G.; Tagliapietra, S. *Tetrahedron: Asymmetry* **2001**, *12*, 707.
16. (a) Halland, N.; Hansen, T.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4955; (b) Kim, H.; Yen, C.; Preston, P.; Chin, J. *Org. Lett.* **2006**, *8*, 5239; (c) Xie, J. W.; Yue, L.; Chen, W.; Du, W.; Zhu, J.; Deng, J. G.; Chen, Y. C. *Org. Lett.* **2007**, *9*, 413; (d) Dong, Z.; Wang, L.; Chen, X.; Liu, X.; Lin, L.; Feng, X. *Eur. J. Org. Chem.* **2009**, 5192; (e) Kristensen, T. E.; Vestli, K.; Hansen, F. K.; Hansen, T. *Eur. J. Org. Chem.* **2009**, 5185.
17. (a) Yang, L.; Xu, L. W.; Xia, C. G. *Tetrahedron Lett.* **2007**, *48*, 1599; (b) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2009**, *38*, 2745. and references cited therein.
18. (a) Ju, Y. D.; Xu, L. W.; Li, L.; Lai, G. Q.; Qiu, H. Y.; Jiang, J. X.; Lu, Y. *Tetrahedron Lett.* **2008**, *49*, 6773; (b) Jiang, Z. Y.; Yang, H. M.; Ju, Y. D.; Li, L.; Luo, M. X.; Lai, G. Q.; Jiang, J. X.; Xu, L. W. *Molecules* **2010**, *15*, 2551.
19. Morris, D. J.; Partridge, A. S.; Manville, C. V.; Racys, D. T.; Woodward, G.; Docherty, G.; Wills, M. *Tetrahedron Lett.* **2010**, *51*, 209.