Tetrahedron Letters 53 (2012) 3349–3352

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Synthesis of functionalized and fused furans and pyrans from the Morita–Baylis–Hillman acetates of nitroalkenes

Divya K. Nair, Shaikh M. Mobin, Irishi N.N. Namboothiri *

Department of Chemistry, Indian Institute of Technology, Bombay, Mumbai 400 076, India

ARTICLE INFO

Article history:
Received 14 March 2012
Revised 18 April 2012
Accepted 18 April 2012
Available online 25 April 2012

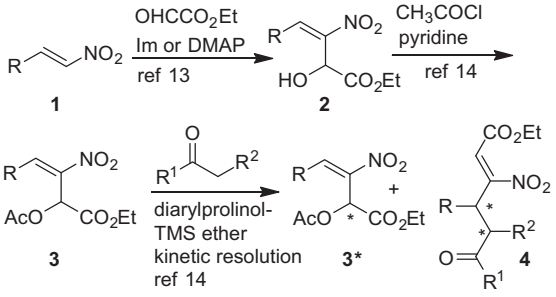
Keywords:
Furan
Pyran
Nitroalkene
Morita–Baylis–Hillman acetates
Cascade reaction

ABSTRACT

The Morita–Baylis–Hillman (MBH) acetates derived from nitroalkenes and ethyl glyoxylate have been transformed in one pot at room temperature to highly fused and functionalized furans and pyrans in good to excellent yield. The reaction involves a cascade Michael–oxa-Michael addition of β-dicarbonyl compounds to the MBH acetates in the presence of an amine base such as DABCO. An unusual switching of selectivity in the oxa-Michael addition from 5-*exo*-trig to 6-*endo*-trig was observed when the β-dicarbonyl compound was changed from acyclic or six-membered ring cyclic to five-membered ring cyclic system.

Functionalized and fused furans are fabulous heterocyclic scaffolds for the synthesis of numerous natural products and designed molecules.[1] The biological activities such as anti-microbial, anti-cancer, and tubulin binding properties of furan containing compounds are well-documented in the literature.[2] This exceptional ability of furans to function as synthetic intermediates and as biological agents endowed them as one of the sought after heterocycles in organic synthesis.[3] The cyclocondensation of 1,4-dicarbonyl compounds (Paal–Knorr synthesis)[4] and that of α-haloketones or analogous compounds with β-dicarbonyl compounds (Feist–Benary synthesis)[5] is the classical method for the synthesis of furans. In recent years, transition metal-mediated cycloisomerization of alkynyl and allenyl substrates has emerged as an efficient strategy.[6] However, development of new protocols for the synthesis of furans from readily available precursors under mild conditions is still an attractive objective.

Although pyran skeleton is present in sugars, flavanoids, and other natural products, 4*H*-pyrans received only a limited attention.[7] Sporadic reports on the biological activities of 4*H*-pyrans indicate their ability to function as inhibitors of influenza virus sialidases and as plant growth stimulants.[8] The well known methods of intramolecular cyclization of *o*-hydroxychalcones (Auwers synthesis), rearrangement of aromatic *o*-ketoesters of phenols (Baker–Venkataraman synthesis), condensation of phenols with β-ketoesters (von Pechman synthesis), and condensation of *o*-hydroxyarylketones with enamines or carbonyl compounds (Kabe synthesis and Robinson–Kostanecki synthesis) are all limited to the synthesis of chromones (benzopyranones).[9] To our knowledge, the available methods for the synthesis of 4*H*-pyrans are too substrate specific[7,10] and 4*H*-pyrans fused to other alicycles are relatively rare.[11]



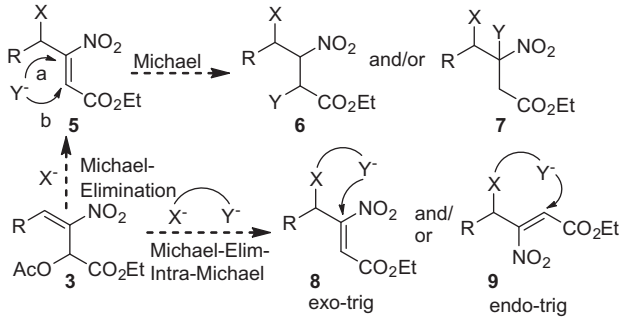
Scheme 1. Previous work.

The Morita–Baylis–Hillman (MBH) reaction between electron deficient alkenes and suitable carbonyl compounds generates a diverse array of allylic alcohols that are amenable for further manipulation.[12] Some time ago, we reported the MBH reaction of nitroalkenes **1** with various activated non-enolizable carbonyl compounds, for instance, ethyl glyoxylate, to generate alcohols **2** (Scheme 1).[13] Recently, Chen and co-workers elegantly demonstrated the kinetic resolution of corresponding acetates **3** using aldehydes and ketones involving a Michael addition-elimination sequence.[14]

We realized that at least two potential electrophilic sites open up as in **5** or **8–9** after the first Michael addition to acetate **3** followed

* Corresponding author.
E-mail address: irishi@iitb.ac.in (I.N.N. Namboothiri).

0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.04.084



Scheme 2. Present work.

by elimination offering the possibility of further Michael addition (Scheme 2). Such a second Michael addition in an intermolecular fashion would provide **6** or **7** whereas its intramolecular version would take place in an *n-exo*-trig fashion as shown in **8** and/or in an *n*+1-*endo*-trig fashion as in **9**. The intramolecular version would be particularly attractive from the perspective of synthesis of densely functionalized and fused heterocyclic scaffolds. We envisioned that β-dicarbonyl compounds would be excellent nucleophiles to test our hypothesis due to their proven ability to enolize and react as C-nucleophiles and as oxygen nucleophiles under suitable conditions.[15]

Initially, MBH acetate **3a** and dimedone **10** were chosen as model substrates for our studies. Treatment of **3a** with **10** in the presence of 1 equiv of amine bases such as DMAP, DBU, imidazole, and Et_3N in THF at room temperature provided unsatisfactory results (Table 1, entries 1–4). However, when **3a** was treated with **10** in the presence of DIPA, we were pleasantly surprised to see the formation of furan **11a** in 52% yield (Table 1, entry 5). Further improvement in the yield was observed in the presence of K_2CO_3 and EDIPA (63% and 70%, respectively, Table 2, entries 6–7). Finally, a remarkable increase in the yield (92%) with decrease in reaction time (1 h) was observed when the reaction was carried out in the presence of 1 equiv of DABCO (Table 1, entry 8). Longer reaction time (10 h) and substantial decrease in the yield (72%) were encountered when the amount of DABCO was reduced to 0.5 equiv (Table 1, entry 9).

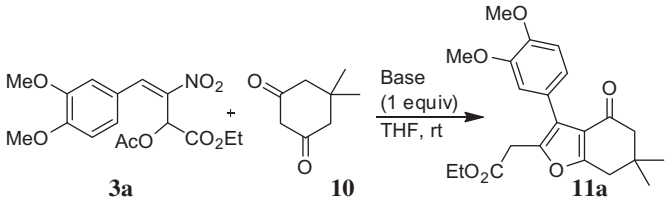
The above optimized conditions, viz. 1 equiv of DABCO, in THF, at rt, were employed to explore the scope of the reaction of dimedone **10** with different MBH acetates **3b–m** (Table 2). It is important to note that the MBH acetates with strong single and multiple electron donating groups on the aromatic rings **3a–3f** provide the products **11a–f** in excellent yield (>90%, Table 3, entries 1–6). The MBH acetates with aromatic rings possessing weakly activating and weakly deactivating substituents, **3g** and **3i,** respectively, as well as those with phenyl and heteroaromatic rings, **3h** and **3j–k**, respectively, delivered the desired furans in high yield (85–88%, Table 2, entries 7–11). Marginally lower yield (75%) was encountered when nitrodiene derived MBH acetate **3l** was employed as the Michael acceptor (Table 2, entry 12). However, our attempts to react the acetate **3m** with dimedone **10** under the optimized conditions provided only complex mixture (Table 2, entry 13).

The hallmark of the above strategy was the formation of regioisomerically pure products at rt in good to excellent yields in reaction times not exceeding 6 h. The regiochemistry of the products was confirmed by ^{1}H–1H NOESY experiment. Thus a positive NOE interaction was observed between CH_2 appearing as a singlet at δ 3.69 and the aromatic protons in a representative compound **11d**. The structure of furans **11a–l** was further unambiguously established by single crystal X-ray analysis of a representative product **11j** (see Supplementary data).

Further scope of the above Michael–oxa–Michael-elimination cascade was investigated by the addition of diverse acyclic and six-membered cyclic β-dicarbonyl compounds **12a–f** to a representative MBH acetate **3d** under the optimized conditions (Table 3). Thus β-diketones viz. cyclohexanedione **12a** and acetylacetone **12b** reacted with MBH acetate **3d** to provide furans **13a** and **13b** in yields of 88% and 92%, respectively (Table 3, entries 1–2). An acyclic β-diketone with extended conjugation such as **12c** (analog of curcumin) afforded the embellished furan **13c** though in lower yield (54%) and a longer reaction time (48 h, Table 3, entry 3). Similar reaction of β-ketoester **12d** with MBH acetate **3d** proceeded well to provide furan **13d** in good yield (Table 4, entry 4). However, under our experimental conditions, the cyclic ester, Meldrum's acid, **12e** did not add to MBH acetate **3d** and the cyclic diamide, barbituric acid, **12f**, though reacted with **3d**, gave an intractable mixture on attempted purification (Table 3, entry 6).

Surprisingly, reaction of a series of MBH acetates **3** with cyclopentanedione **14** under the above optimized conditions led to the formation of fused pyrans **15** instead of furans as observed in the

Table 1
Screening of bases

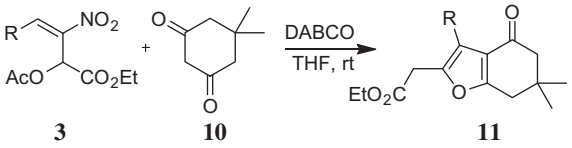


3a 10 11a

Entry	Base	Time (h)	Yield (%)[a]
1	DMAP	6	Traces
2	DBU	1	Complex mixture
3	Imidazole	16	No reaction
4	Et_3N	30	Complex mixture
5	DIPA	4	52
6	K_2CO_3	1	63
7	EDIPA	5	70
8	**DABCO**	**1**	**92**
9	DABCO[b]	10	72

[a] Isolated yield after silica gel column chromatography.
[b] 0.5 equiv of DABCO was used.

Table 2
Synthesis of fused furans **11** via addition of dimedone **10** to MBH acetates **3**



3 10 11

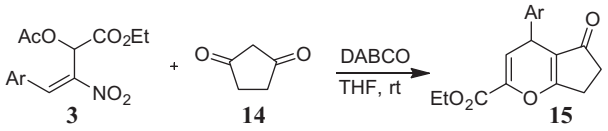
Entry	R	11	Time (h)	% Yield[a]
1	3,4-$(OMe)_2$Ph	**11a**	1	92
2	2,5-$(OMe)_2$Ph	**11b**	2.5	90
3	3,4-(OCH_2O)Ph	**11c**	1	94
4	3,4,5-$(OMe)_3$Ph	**11d**	1	94
5	4-OMePh	**11e**	1	91
6	4-NMe_2Ph	**11f**	6	94
7	4-MePh	**11g**	5	87
8	Ph	**11h**	1.5	88
9	4-ClPh	**11i**	1.5	86
10	2-Furyl	**11j**	3	85
11	2-Thienyl	**11k**	2.5	86
12	2-MeOPhCH=CH	**11l**	1	75
13	*i*-Pr	**11m**	1	—[b]

[a] Isolated yield after silica gel column chromatography.
[b] Complex mixture.

case of acyclic and six-membered cyclic β-dicarbonyl compounds (Table 4). The MBH acetates with strongly electron donating aromatic rings **3a** and **3c** and those with heteroaromatic rings **3j** and **3k** reacted with **14** to afford pyrans **15a**, **15c**, **15j,** and **15k**, respectively, in good yield (72–81%, Table 4, entries 1, 2, 5, and 6). Although MBH acetate **3h** with Ph group at the β-position of the nitro group gave the product in moderate yield (53%, entry 3), the corresponding *p*-chlorophenyl analog **3i** reacted well with **14** to give pyran **15i** in good yield. The structure of pyrans **15a**, **15c,** and **15h–k** was confirmed by single crystal X-ray analysis of a representative product **15k** (see Supplementary data).

The proposed mechanism involves DABCO mediated deprotonation of β-dicarbonyl compound, for example, **12a** or **14**, and its addition to MBH acetate **3** in a Michael fashion which is overall an S_N2' substitution (Scheme 3). The intermediate **I** or **III** then undergoes enolization followed by intramolecular oxa-Michael addition in a regioselective fashion. In the case of dimedone **10** or six-membered cyclic or open chain β-dicarbonyl compound **12**, oxa-Michael addition in a 5-*exo*-trig fashion to the α,β-unsaturated ester moiety affords intermediate **II** (path A, Scheme 3). The DABCO mediated elimination of HNO_2 from intermediate **II** completes the sequence to provide a highly functionalized and fused furan **11**. In the case of cyclopentanedione **14**, although the first step is analogous to that in the furan formation, a dramatic change in the reaction profile is observed in the second step (path B,

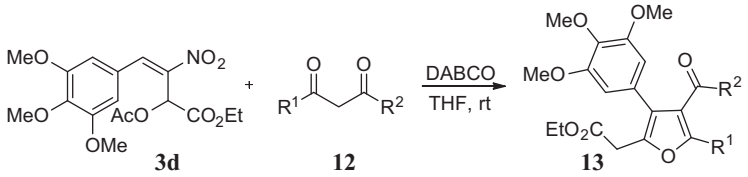
Table 4
Synthesis of fused pyrans **15** via reaction of cyclopentan-1,3-dione **14** with MBH acetates **3**

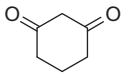
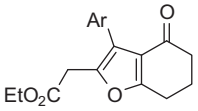
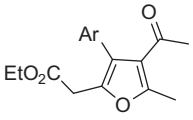
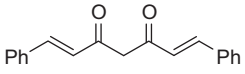
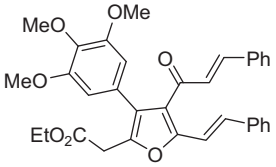
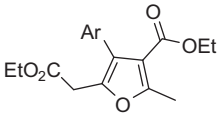
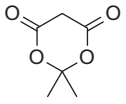
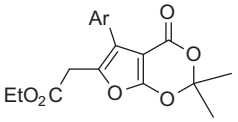
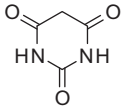
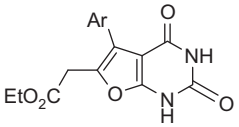


Entry	Ar	15	Time (h)	% Yield[a]
1	3,4-$(OMe)_2$Ph	**15a**	5	81
2	3,4-(OCH_2O)Ph	**15c**	4	72
3	Ph	**15h**	4	53
4	4-ClPh	**15i**	1	70
5	2-Furyl	**15j**	6	80
6	2-Thienyl	**15k**	4	78

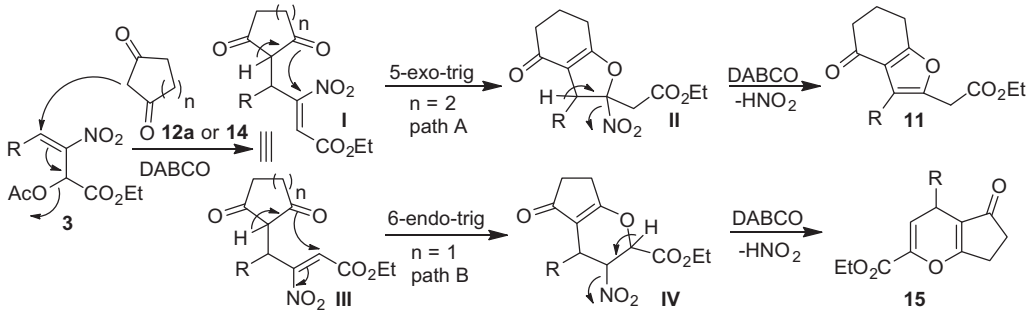
[a] Isolated yield after silica gel column chromatography.

Table 3
Scope of acyclic and six-membered cyclic 1,3-dicarbonyl compounds **12**



Entry	12	1,3-Dicarbonyls	13	Furans	Time (h)	% Yield[a]
1	**12a**		**13a**		4	88
2	**12b**	R^1, $R^2 = CH_3$	**13b**		1	92
3	**12c**		**13c**		48	54
4	**12d**	$R^1 = CH_3$, $R^2 = OEt$	**13d**		3	74
5	**12e**		**13e**		24	—[b]
6	**12f**		**13f**		4	—[c]

[a] Isolated yield after silica gel column chromatography.
[b] No reaction.
[c] Complex mixture.



Scheme 3. Proposed mechanism for the formation of furans **11**, **13,** and pyrans **15**.

Scheme 3). Thus the oxa-Michael addition in **III** is not to the α,β-unsaturated ester moiety, but to the nitroalkene moiety in a 6-*endo*-trig fashion. This dramatic change in the mode of cyclization is attributable to a combination of the geometry of the enolate arising from **III** and the superior Michael acceptor ability of nitroalkene moiety (Scheme 3).

In conclusion, highly regioselective cascade reactions of β-dicarbonyl compounds with Morita–Baylis–Hillman acetates of nitroalkenes led to functionalized and fused furans and pyrans in high yield. The reaction mediated by DABCO proceeds in a cascade Michael–5-*exo*-trig-oxa-Michael fashion in the case of open chain and six-membered cyclic β-dicarbonyl compounds to afford fused furans. On the other hand, a cascade Michael–5-*endo*-trig-oxa-Michael reaction takes place in the case of five-membered cyclic β-dicarbonyl compounds to afford fused 4*H*-pyrans.

Acknowledgment

I.N.N.N. thanks the DST India for financial assistance. D.K.N. thanks the CSIR India for a senior research fellowship. The authors thank the CRNTS, IIT Bombay for selected NMR data.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.04.084.

References and Notes

1. (a) Keay, B. A.; Dibble, P. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Sciven, E. F. V., Eds.; Elsevier: Oxford, 1997; Vol. 2, p 395; (b) Donnelly, D. M. X.; Meegan, M. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 4, p 657.
2. Anti-microbial: (a) Zanatta, N.; Alves, S. H.; Coelho, H. S.; Borchhardt, D. M.; Machado, P.; Flores, K. M.; Silva, F. M.; Spader, T. B.; Santurio, J. M.; Bonacorso, H. G.; Martins, M. A. P. *Bioorg. Med. Chem.* **2007**, *15*, 1947; (b) Khan, M. W.; Alam, M. J.; Rashid, M. A.; Chowdhury, R. *Bioorg. Med. Chem.* **2005**, *13*, 4796; Anticancer: (c) Rao, R. R.; Chaturvedi, V.; Babu, K. S.; Reddy, P. P.; Rao, V. R. S.; Sreekanth, P.; Sreedhar, A. S.; Rao, J. M. *Med. Chem. Res.* **2012**, *21*, 634; Tubulin polymerization inhibitor: (d) Kerr, D. J.; Hamel, E.; Jung, M. K.; Flynn, B. L. *Bioorg. Med. Chem.* **2007**, *15*, 3290.
3. For recent reviews, see: (a) Brown, R. C. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 850; (b) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. *Tetrahedron* **1998**, *54*, 1955; (c) Kirsch, S. F. *Org. Biomol. Chem.* **2006**, *4*, 2076.
4. (a) Amarnath, V.; Amarnath, K. *J. Org. Chem.* **1995**, *60*, 301; (b) Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M. *Eur. J. Org. Chem.* **2005**, 5277.
5. (a) Feist, F. *Chem. Ber.* **1902**, *35*, 1537; (b) Benary, E. *Chem. Ber.* **1911**, *44*, 489; (c) Mross, G.; Holtz, E.; Langer, P. *J. Org. Chem.* **2006**, *71*, 8045; (d) Ayyagari, N.; Jose, D.; Mobin, S. M.; Namboothiri, I. N. N. *Tetrahedron Lett.* **2011**, *52*, 258.
6. (a) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285; (b) Ma, S.; Zhang, J.; Lu, L. *Chem. Eur. J.* **2003**, *9*, 2447; (c) Marshall, J. A.; Bartley, G. S. *J. Org. Chem.* **1994**, *59*, 7169; (d) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 5195; (e) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **1995**, *34*, 1581.
7. Reviews: (a) Santamaria, J.; Valdes, C. In *Modern Heterocyclic Chemistry*, Alvarez-Builla, J.; Vaquero, J. J.; Barluenga, J., Eds.; 2011, Vol. 3, p 1631.; (b) Litvinov, Y. M.; Shestopalov, A. M. *Adv. Heterocycl. Chem.* **2011**, *103*, 175; (c) Shestopalov, A. M.; Emel'yanova, Y. M. In *Izbrannye Metody Sinteza i Modifikatsii Geterotsiklov*, Kartsev, V. G., ed.; 2003, Vol. 2, p 534.; (d) Martin, N.; Quinteiro, M.; Seoane, C.; Soto, J. L. *Afinidad* **1993**, *50*, 389; (e) Drygina, O. V.; Garnovskii, A. D. *Khimiya Geterotsiklicheskikh Soedinenii* **1983**, 1011; (f) Seoane, C.; Soto, J. L.; Quinteiro, M. *Heterocycles* **1980**, *14*, 337.
8. Influenza virus inhibitor: (a) Smith, P. W.; Sollis, S. L.; Howes, P. D.; Cherry, P. C.; Starkey, I. D.; Cobley, K. N.; Weston, H.; Scicinski, J.; Merritt, A.; Whittington, A. *J. Med. Chem.* **1998**, *41*, 787; (b) Plant growth stimulant: Zamocka, J.; Misikova, E. *Slovakia* **1995**, SK 277932 B6 19950809.; (c) Veverka, M. *Chem. Papers* **1992**, *46*, 206; (d) Vardaro, R. R.; Di Marzo, V.; Marin, A.; Cimino, G. *Tetrahedron* **1992**, *48*, 9561.
9. Hassner, A.; Namboothiri, I. Eds., In *Organic Syntheses Based on Name Reactions, A Practical Guide to 750 Transformations*, 3rd ed.; Elsevier: Oxford, UK, 2012.
10. (a) Adam, W.; Berkessel, A. *Chem. Ber.* **1985**, *118*, 5018; (b) Shi, J.; Wang, M.; He, L.; Zheng, K.; Liu, X.; Lin, L.; Feng, X. *Chem. Commun.* **2009**, 4711.
11. Imagawa, H.; Kotani, S.; Nishizawa, M. *Synlett* **2006**, 642.
12. Selected recent reviews: (a) Basavaiah, D.; Veeraraghavaiah, G. *Chem. Soc. Rev.* **2012**, *41*, 68; (b) Basavaiah, D.; Reddy, B. S.; Badsara, S. S. *Chem. Rev.* **2010**, *110*, 5447; (c) Rios, R. *Catal. Sci. Tech.* **2012**, *2*, 267.
13. (a) Deb, I.; Dadwal, M.; Mobin, S. M.; Namboothiri, I. N. N. *Org. Lett.* **2006**, *8*, 1201; (b) Deb, I.; Shanbhag, P.; Mobin, S. M.; Namboothiri, I. N. N. *Eur. J. Org. Chem.* **2009**, 4091.
14. (a) Reddy, R. J.; Chen, K. *Org. Lett.* **2011**, *13*, 1458; (b) Reddy, R. J.; Lee, P. H.; Magar, D. R.; Chen, J. H.; Chen, K. *Eur. J. Org. Chem.* **2012**, 353.
15. While proceeding with the submission of this manuscript, we noticed a closely related work having just appeared: Huang, W.-Y.; Chen, Y.-C.; Chen, K. *Chem. Asian J.* **2012**, *7*, 688.