CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.201000907

Copper-Catalysed Domino Silylative Aldol Reaction Leading to Stereocontrolled Chiral Quaternary Carbons

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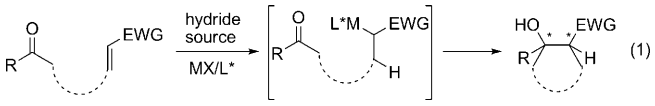
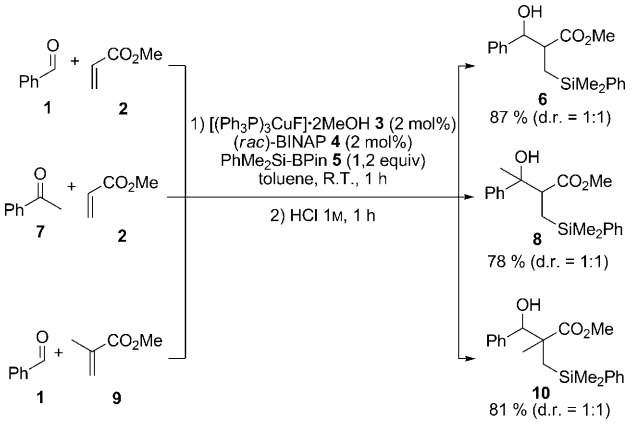
Domino reactions are processes in which several bonds are formed in one step without isolating intermediates, changing the conditions of the reaction or adding reagents.[1] These reactions are ecologically and economically favourable because work, time and materials are spared. Amongst domino reactions, the reductive aldol reaction has been developed as an efficient alternative one-pot procedures for the production of aldol derivatives without the need to generate a metal enolate prior to the condensation with an aldehyde or a ketone. Versions based on various transition-metal catalysts[2] have been reported, in particular with copper.[3] Since the pioneering work of Maruoka[4] and Chiu,[5] intramolecular racemic[6] and enantioselective,[7] as well as intermolecular racemic[8] and enantioselective[9] methods, have been developed based on this metal. These reactions are proposed to proceed by the in situ formation of a metal enolate through the conjugated reduction of a metal hydride species onto the Michael acceptor as described in [Eq. (1)]. Then, the generated nucleophile is trapped by the electrophile to form the aldol-type adduct after final reaction with the hydride source.

We were interested in applying this methodology with borosilanes as pronucleophiles. The addition of this family of reagents catalysed by Pd, Rh or Pt is well documented.[10]



Copper(I) catalysts have been show to catalyse the conjugated addition of disilane[11] and silylmetal nucleophiles[12] on electrophilic double bonds. Although the use of disilanes requires harsh conditions to proceed, the use of silyl–metal species is not suitable for silylative aldol because of potential direct addition of the silyl group to the aldehyde. This problem of chemoselectivity is well known in copper hydride chemistry.[7d,9e] Recently, an asymmetric conjugated addition of borosilanes on electrophilic double bonds with high enantioselectivities was reported by Hoveyda by using chiral copper–diaminocarbene complexes with an example of a tandem aldol reaction.[13]

In our initial experiments (Scheme 1) we tested the three-component domino reaction between benzaldehyde **1**, methyl acrylate **2** and a stoichiometric quantity of borosilane[15] **5** in toluene at room temperature in the presence of a catalytic amount of $[CuF(PPh_3)_3]\cdot 2MeOH$[14] **3**, and (*rac*)-



Scheme 1. Initial experiments for copper-catalysed silylative aldol reactions.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201000907.

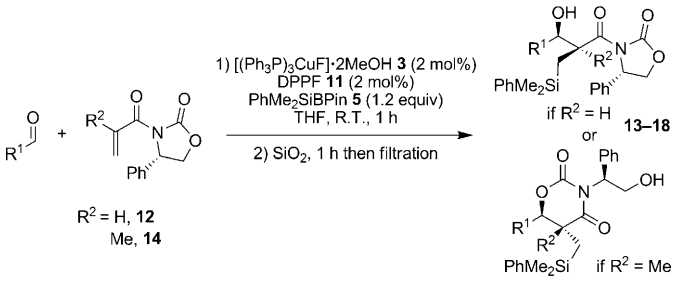
BINAP ((*rac*)-BINAP: racemic 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) **4** (Scheme 1). The corresponding aldol adduct **6** was isolated in 87% yield, albeit without any diastereoselectivity. Replacing benzaldehyde **1** by acetophenone **7** led to the tertiary chiral alcohol **8** in 78% yield. Switching methyl acrylate **2** to methyl methacrylate **9** gave compound **10**, which has a chiral quaternary carbon in 81% yield. Although no diastereoselectivities were observed with these substrates, we observed an excellent reactivity of our catalytic system because excellent yields of the three component adducts were obtained in each case with low catalyst loading and short reaction time.

The use of methyl methacrylate **9** as an enolate precursor and acetophenone **7** as the aldol partner are particularly striking. It indeed allows the formation of either tertiary alcohols (such as in **8**) or quaternary chiral centres (such as in **10**) in a single catalytic reaction and starting from simple substrates. The control of the stereochemistry of chiral quaternary centres is one of the major challenge of organic methodology and there are still few reported examples of efficient methodologies that use the aldol condensation.[16,17]

Our hypothesis was that the stereochemistry could be controlled by using chiral auxiliaries such as oxazolidinones on the Michael acceptors. After optimisation of the catalytic system and a survey of various achiral diphosphine ligands, we found that better reproducibility was achieved by replacing (*rac*)-BINAP **4** by DPPF (DPPF : 1,1′-bis(diphenylphosphino)ferrocene) **11** when the reaction was carried out in THF instead of toluene (Table 1). Moreover, aqueous work-up may be avoided by adding silica to the reaction medium followed by a simple filtration on silica gel. Prior to investigating the formation of quaternary carbon centres, we evaluated simple chiral acryloyl-based Michael acceptors and obtained very promising results with acceptor **12**. We were indeed pleased to find that under the optimised catalytic conditions, the reaction between benzaldehyde **1** and acryloyloxazolidinone **12** (Table 1, entry 1) gave the corresponding *syn*-aldol adduct (*syn*/*anti* > 95:5 by ^{1}H NMR analysis on the crude reaction mixture) **13** in 80% yield and with a complete control of the stereochemistry (d.r. > 95:5). We next investigated the substrate generality with other aromatic aldehydes (Table 1, entries 2–4). Electron-rich aromatic aldehydes (Table 1, entries 2 and 3) led to good yields but reduced diastereoselectivities. With a more electron-poor aldehyde (Table 1, entry 4) the yield was slightly lower and the diastereoselectivity was excellent. The absolute configuration of compound **16** was determined by X-ray diffraction (Figure 1). We have assumed that the absolute configurations are the same through the examples considered.

We next investigated the use of methacryloyloxazolidinone **14** (Table 1, entries 5–12). This Michael acceptor reacted with the silylboronate and benzaldehyde under the optimised catalytic conditions (Table 1, entry 5) to afford the corresponding adduct **19** in excellent yield and only one diastereoisomers was detected in the NMR spectrum of the crude reaction mixture. The structure of the aldol adduct was first attributed to a simple open structure such as **25**

Table 1. Copper-catalysed silylative–aldol reaction between enoyloxazolidinones and various aldehydes[a]



Entry	R^1	R^2	Yield (%)[b]	d.r.[c]	Product
1	C_6H_5	H	80	> 95:5	**13**
2	3,5-(tBu)$_2$-C_6H_3	H	79	83:17	**16**
3	4-MeO-C_6H_4	H	70	86:14	**17**
4	4-F-C_6H_4	H	59	> 95:5	**18**
5	C_6H_5	Me	90	> 95:5	**19**
6	3,5(tBu)$_2$-C_6H_3	Me	77	81:19	**20**
7	4-MeO-C_6H_4	Me	69	88:12	**21**
8	4-F-C_6H_4	Me	64	92:8	**22**
9	3,5(CF_3)$_2$-C_6H_3	Me	61	90:10	**23**
10	4-CN-C_6H_4	Me	59	87:13	**24**
11	2-Furyl	Me	75	86:14	**25**
12	2-Thienyl	Me	74	78:22	**26**

[a] The reactions were carried out on a 0.5 mmol scale in a 0.2 M solution in THF at room temperature under an oxygen-free argon atmosphere in the presence of [CuF(PPh$_3$)$_3$]·2MeOH (2 mol%), DPPF (2 mol%), borosilane (1.2 equiv), aldehyde (1 equiv) and enoyloxazolydinone (1 equiv) for 1 h. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis.

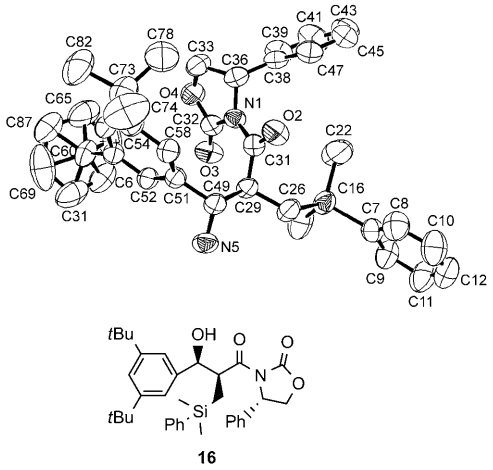


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Figure 1. 50% Thermal ellipsoids structure of **16**.

(Figure 2, X = H) but a rearranged structure was later attributed when an X-xay crystal-structure analysis of the 2-furyl carboxaldehyde adduct was carried out to analyse the absolute configuration of the newly formed asymmetric carbon centres. The rearranged adduct **28** (X = H) is assumed to arise from an intramolecular ring opening of the oxazolidone moiety by the hydroxyl group of the aldol adduct. Although we can assume that a strong Thorpe–Ingold effect brought by the newly formed quaternary carbon centre

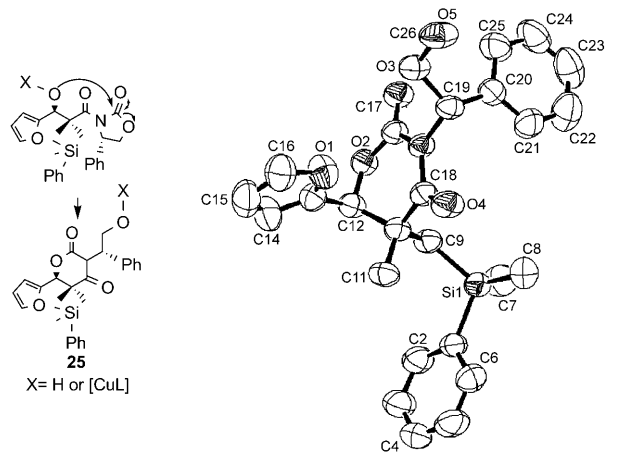

Figure 2. 50% Thermal ellipsoids structure of **25** (X = H).

strongly favoured this ring-opening–cyclisation rearrangement process, it is not clear whether this rearrangement occurs immediately after the aldol condensation (Figure 2, X = [CuL]) or during the work-up of the reaction (Figure 2, X = H). The influence of electronic parameters was then checked with various aromatic and heteroaromatic aldehydes. Moderate to excellent isolated yields were obtained (59–90%) and diastereoselectivities in the range of 78:22 to > 95:5 were achieved. This means that the absolute stereochemistry of the all-carbons chiral quaternary centre is controlled. Electron-rich aromatic aldehydes (Table 1, entries 6 and 7) led to good yields and slightly reduced selectivities. Electron-poor aromatic aldehydes (Table 1, entries 8–10) gave reduced yields but better diastereomeric ratios. With electron-rich heteroaromatic aldehydes (Table 1, entries 11 and 12), good yields were obtained but the selectivities were lower, in particular with thiophene-2-carbaldehyde **27**.

We finally investigated the effect of the structure of the chiral auxiliary (Scheme 2). The optimisation was carried out with thiophene-2-carbaldehyde **27** as the electrophile be-

Scheme 2. Chiral auxiliary structure optimisation.

cause it gave the lowest diastereomeric ratio. The selectivity is dependent on the steric hindrance because the benzyl-substituted substrate **29** led to a lower selectivity. The isopropyl-substituted oxazolidinone **30** led to an improved d.r. and the *tert*-butyl derivative **31** restored the full control of the selectivity.

The true mechanism of this effective and selective domino process is still unclear and should be carefully investigated because the true nature of the reactive intermediates has not yet been identified. The conjugated addition of a copper-bound silyl nucleophile on the chiral Michael acceptor such as **12** is expected to yield an intermediate copper enolate, which should in turn be expected to react with an aldehyde. The stererochemistry obtained with the acryloyloxazolidinone derivative **12** suggests the formation of a *Z*-copper enolate and a classical cyclic Evans transition state.[18] However, care should be taken with such a model because copper(I) is known to be a weak Lewis acid and a chelation model might be rendered unlikely by this property. Furthermore, we cannot exclude the intervention of a boron enolate, which could arise from a fast reaction of the copper enolate with the silylboron reagent **5**. However, we have not yet been able to isolate a boron enolate to check its reactivity and test this hypothesis. In summary, we have developed a domino silylation–aldol reaction between enoyloxazolidinones and various aldehydes. The process catalysed by a copper–phosphane complex in the presence of a borosilane led to high diastereoselectivities. Yields between 59 and 90% and d.r. between 78:22 to 95:5 were obtained. When methacryloyloxazolidinones were used, a controlled chiral quaternary carbon was generated. Absolute configurations were confirmed unambiguously by X-ray diffraction. The diastereoselectivity was improved by replacing the phenyl by a *tert*-butyl group on the chiral auxiliary. Work is now in progress to study the replacement of the silyl group on the enantiopure adducts to broaden the scope of application of those aldol adducts that have quaternary centres.[19] Efforts will be also be carried out to investigate the true mechanism of this reaction and the nature of the enolate intermediate that is responsible for the high stereoselectivity of the aldol condensation.

Acknowledgements

This work was supported by the Université Catholique de Louvain and FNRS.

Keywords: aldol reaction · asymmetric synthesis · copper · quaternary stereocenters · silylation

[1] For reviews on domino reactions, see: a) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; b) D. E. Fogg, E. N. dos Santos, *Coord. Chem. Rev.* **2004**, *248*, 2365–2379; c) C. J. Chapman, C. G. Frost, *Synlett* **2007**, 1–21.

[2] For a review on reductive aldol reactions, see: a) H. Nishiyama, T. Shiomi, *Top. Curr. Chem.* **2007**, *279*, 105–137; b) S. B. Han, A. Hassan, M. J. Krische, *Synlett* **2008**, 2669–2679; for recent examples based on Rh, see: c) T. Shiomi, T. Adachi, J.-I. Ito, H. Nishiyama, *Org. Lett.* **2009**, *11*, 1011–1014; d) K. Murakami,, H. Ohmiya, H. Yorimitsu, K. Oshima, *Tetrahedron Lett.* **2008**, *49*, 2388–2390; based on Ni, see: e) P. M. Joensuu, G. J. Murray, E. A. F. Fordyce, T. Luebbers, H. W. Lam, *J. Am. Chem. Soc.* **2008**, *130*, 7328–7338; based on Co, see: f) R. J. R. Lumby, P. M. Joensuu, H. W. Lam, *Org. Lett.*

2007, *9*, 4367–4370; g) R. J. R. Lumby, P. M. Joensuu, H. W. Lam, *Tetrahedron* **2008**, *64*, 7729–7740.

[3] For reviews with Cu-catalysed domino reactions, see: a) S. Rendler, M. Oestreich, *Angew. Chem.* **2007**, *119*, 504–510; *Angew. Chem. Int. Ed.* **2007**, *46*, 498–504; b) C. Deutsch, N. Krause, B. H Lipshutz, *Chem. Rev.* **2008**, *108*, 2916–2927; c) M. Shibasaki, . M. Kanai, *Chem. Rev.* **2008**, *108*, 2853–2873; d) O. Riant, *Copper(I) Hydride Reagents and Catalysts in The Chemistry of Organocopper Compounds* (Ed.: Z. Rappoport, I. Marek), Wiley, New York, **2009**, pp. 731–774.

[4] T. Ooi, K. Doda, D. Sakai, K. Maruoka, *Tetrahedron Lett.* **1999**, *40*, 2133–2136.

[5] P. Chiu, B. Chen, K. F. Cheng, *Tetrahedron Lett.* **1998**, *39*, 9229–9232.

[6] For diastereoselective reductive aldol reactions mediated by Stryker's reagent, see: a) P. Chiu, B. Chen, K. F. Cheng, *Tetrahedron Lett.* **1998**, *39*, 9229–9232; b) P. Chiu, C. P. Szeto, Z. Geng, K. F. Cheng, *Org. Lett.* **2001**, *3*, 1901–1903; c) P. Chiu, C. P. Szeto, Z. Geng, K. F. Cheng, *Tetrahedron Lett.* **2001**, *42*, 4091–4093; d) P. Chiu, S. K. Leung, *Chem. Commun.* **2004**, 2308–2309; e) W. K. Chung, P. Chiu, *Synlett* **2005**, 55–58.

[7] For enantioselective reductive aldol cyclization catalysed by copper complexes, see: a) K. Agapiou, D. F. Cauble, M. J. Krische, *J. Am. Chem. Soc.* **2004**, *126*, 4528–4529; b) H. W. Lam, P. M. Joensuu, *Org. Lett.* **2005**, *7*, 4225–4228; c) H. W. Lam, G. J. Murray, J. D. Firth, *Org. Lett.* **2005**, *7*, 5743–5746; d) B. H. Lipshutz, B. Amorelli, J. B. Unger, *J. Am. Chem. Soc.* **2008**, *130*, 14378–14379; e) J. Deschamp, O. Riant, *Org. Lett.* **2009**, *11*, 1217–1220; f) C. L. Oswald, J. A. Peterson, H. W. Lam, *Org. Lett.* **2009**, *11*, 4504–4507.

[8] For racemic intermolecular versions, see: A. Welle, S. Diez-Gonzalez, B. Tinant, S. P. Nolan, O. Riant, *Org. Lett.* **2006**, *8*, 6059–6062.

[9] For enantioselecctive intermolecular versions, see: a) J. Deschamp, O. Chuzel, J. Hannedouche, O. Riant, *Angew. Chem.* **2006**, *118*, 1314–1319; *Angew. Chem. Int. Ed.* **2006**, *45*, 1292–1297; b) D. B. Zhao, K. Oisaki, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2006**, *47*, 1403–1407; c) D. Zhao, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 14440–14441; d) K. Oisaki, D. Zhao, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, *128*, 7164–7165; e) O. Chuzel, J. Deschamp, C. Chausteur, O. Riant, *Org. Lett.* **2006**, *8*, 5943–5946; f) Y. Du, L.-W. Xu, Y. Shimizu, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2008**, *130*, 16146–16147; g) I. H. Chen, L. Yin, W. Itano, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 11664–11665; h) M. O. Kato, Hiroshi; K. Ogata, S. Fukuzawa, *Synlett* **2009**, 1299–1302.

[10] For reviews on borosilanes, see: a) T. Ohmura, M. Suginome, *Bull. Chem. Soc. Jpn.* **2009**, *82*, 29–49; b) H. E. Burks, J. P. Morken, *Chem. Commun.* **2007**, 4717–4725. Recent examples: c) C. Walter, G. Auer, M. Oestreich, *Angew. Chem.* **2006**, *118*, 5803–5805; *Angew. Chem. Int. Ed.* **2006**, *45*, 5675–5677; d) H. Ohmiya, H. Ito, M. Sawamura, *Org. Lett.* **2009**, *11*, 5618–5620; e) T. Ohmura, K. Masuda, I. Takase, M. Suginome, *J. Am. Chem. Soc.* **2009**, *131*, 16624–16625; f) T. Ohmura, H. Taniguchi, M. Suginome, *Org. Lett.* **2009**, *11*, 2880–2883; g) C. Walter, R. Fröhlich, M. Oestreich, *Tetrahedron* **2009**, *65*, 5513–5520.

[11] a) H. Ito, T. Ishizuka, J. Tateiwa, M. Sonoda, A. Hosomi, *J. Am. Chem. Soc.* **1998**, *120*, 11196–11197; b) C. T. Clark, J. F. Lake, K. A. Scheidt, *J. Am. Chem. Soc.* **2004**, *126*, 84–85.

[12] a) B. H. Lipshutz, J. A. Sclafani, T. Takanami, *J. Am. Chem. Soc.* **1998**, *120*, 4021–4022; b) M. Oestreich, B. Weiner, *Synlett* **2004**, 2139; c) G. Auer, B. Weiner, M. Oestreich, *Synthesis* **2006**, 2113–2116; for a recent review, see d) A. Weickgenannt, M. Oestreich, *Chem. Eur. J.* **2010**, *16*, 402–412.

[13] K.-s. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2010**, *132*, 2898–2900.

[14] $[CuF(PPh_3)_3]\cdot 2MeOH$ was prepared according to a literature procedure: D. J. Gulliver, W. Levason, M. Webster, *Inorg. Chim. Acta* **1981**, *52*, 153–159.

[15] Prepared according to a literature procedure: M. Suginome, T. Matsuda, Y. Ito, *Organometallics* **2000**, *19*, 4647–4649.

[16] For reviews, seea) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402–415; *Angew. Chem. Int. Ed.* **1998**, *37*, 388–401; b) I. Denissova, L. Barriault, *Tetrahedron* **2003**, *59*, 10105–10146; c) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473–1482; d) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369–396.

[17] a) A. Ando, T. Miura, T. Tatematsu, T. Shiori, *Tetrahedron Lett.* **1993**, *34*, 1507–1510; b) N. Mase, F. Tanaka, C. F. Barbas III, *Angew. Chem.* **2004**, *116*, 2474–2477; *Angew. Chem. Int. Ed.* **2004**, *43*, 2420–2423; c) S. Kobayashi, T. Ogino, H. Shimizu, S. Ishikawa, T. Hamada, K. Manabe, *Org. Lett.* **2005**, *7*, 4729–4731; d) W. Wang, H. Li, J. Wang, *Tetrahedron Lett.* **2005**, *46*, 5077–5079; e) S. E. Denmark, T. W. Wilson, M. T. Burk, J. R. Heemstra, Jr., *J. Am. Chem. Soc.* **2007**, *129*, 14864–14865; f) T. Ichibakase, Y. Orito, M. Nakajima, *Tetrahedron Lett.* **2008**, *49*, 4427–4429; g) G.-L. Zhao, P. Dziedzic, F. Ullah, L. Eriksonn, A. Córdova, *Tetrahedron Lett.* **2009**, *50*, 3458–3462; h) T. Yoshino, H. Morimoto, G. Lu, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 17082–17083; for two selected examples of diastereoseelctive aldol reaction leading to the stereoselective construction of quaternary centres, see: i) S. Yamago, D. Machii, E. Nakamura, *J. Org. Chem.* **1991**, *56*, 2098–2106; j) E. D. Burke, J. L. Gleason, *Org. Lett.* **2004**, *6*, 405–407; for a general alternate method for the stereoselective construction of aldol products with quaternary stereocenters, see: J. P. Das, H. Chechik, I. Marek, *Nat. Chem. Biol.* **2009**, *1*, 128–132.

[18] D. A. Evans, J. V. Nelson, T. R. Taber, *Top. Stereochem.* **1982**, *13*, 1–116.

[19] An attractive application of a domino process for the synthesis of (+)-erysotramidine was recently reported by the group of Tietze: L. F. Tietze, N. Tölle, T. Kratzert, D. Stalke, *Org. Lett.* **2009**, *11*, 5230–5233.

Received: April 11, 2010
Published online: August 4, 2010

