EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201402001

Stereoselective Access to β-*C*-Glycosamines by Nitro-Michael Addition of Organolithium Reagents

Thierry Delaunay,[a] Thomas Poisson,*[a] Philippe Jubault,[a] and Xavier Pannecoucke*[a]

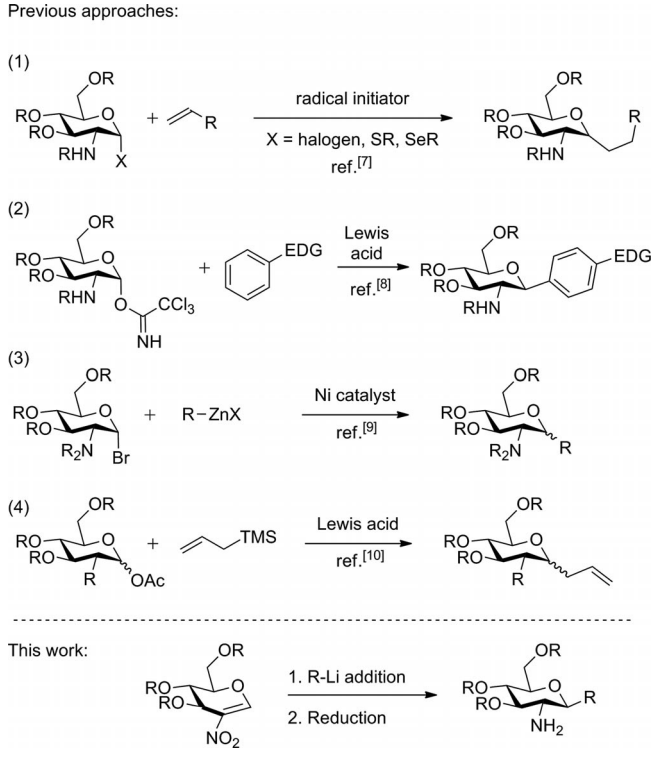
Keywords: Synthetic methods / Michael addition / Lithium / Diastereoselectivity / Carbohydrates

The nitro-Michael addition of organolithium species to 2-nitroglycal derivatives was investigated. This methodology affords straightforward and stereoselective access to *C*-nitroglycosides, which are excellent precursors to *C*–*N*-acetylglycosamines. The corresponding products bearing an aromatic, heteroaromatic, alkynyl, alkenyl, or alkyl moiety were isolated in good yields with excellent selectivities. The β isomer was isolated as a single stereoisomer in most cases, and the structure was clearly elucidated by NMR spectroscopy experiments.

Introduction

Carbohydrates are key components of glycopeptide and glycolipid structures involved in numerous biological processes.[1] Glycoconjugates are present on the cell surface and are involved in several cellular communication events. For instance, glycoproteins have shown a key role in several infections owing to the selective recognition of the glycosidic part of their structure.[2] As a result, carbohydrates are extremely appealing toward the design of new therapeutics such as anticancer drugs.[3] Unfortunately, these potent and promising applications are severely hampered by the low stability of the glycosidic bond in vivo. The most popular way to tackle this major drawback is through the replacement of the oxygen atom with a methylene motif to give non-hydrolizable *C*-glycosides.[4] Indeed, *C*-glycosides are less sensitive to metabolic hydrolysis, and they have been described to possess interesting biological activities as drug candidates and inhibitors of carbohydrate-processing enzymes. Noteworthy, this strategy has been widely explored, which led to the design of several elegant methods towards their synthesis.[5] As part of these *C*-glycosides, β-*C*-aryl glycosides are a very important class of *C*-glycosides that are present in several bioactive and natural compounds.[6]

Among all these carbohydrates, 2-amino-2-deoxysugars are key components of *O*- and *N*-glycopeptides, and the synthesis of their *C*-analogues is appealing to access metabolic-resistant compounds. The developed strategies to access these structures usually focus on (1) radical-based reaction of a halo- or chalcogenoglycoside on olefins,[7] (2) Friedel–Crafts arylation of glycosyl-based acetamidate,[8] (3) metal-catalyzed arylation of haloglycosides,[9] and (4) Lewis acid mediated nucleophilic substitution of an anomeric acetate[10] (Scheme 1).



Scheme 1. State of the art; EDG = electron-donating group.

Results and Discussion

2-Nitroglycals are versatile building blocks for the synthesis of 2-amino-2-deoxyglycosides.[11] Basically, these

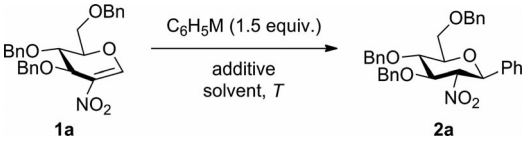
[a] Normandie Univ., COBRA, UMR 6014 et FR 3038, Univ. Rouen, INSA Rouen, CNRS,
1 rue Tesnière, 76821 Mont Saint-Aignan Cedex, France
E-mail: thomas.poisson@insa-rouen.fr
xavier.pannecoucke@insa-rouen.fr
http://www.lab-cobra.fr/

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201402001.

versatile compounds are mainly used in the course of Michael addition reactions with "soft" nucleophiles such as alcohols,[11c–11e] thiols,[11f] malonates,[11g] N-nucleophiles,[11h,11i] and others.[11j–11m] Quite surprisingly, a sole report dealt with the addition of allylzinc and vinylmagnesium species onto this backbone with modest α/β stereoselectivity,[12,13] whereas the addition of lithiated dithiane was reported on a single 2-nitroglucal derivative without a yield and with complete β selectivity.[14]

Herein, we report our efforts towards the development of a nitro-Michael addition of organolithium reagents to 2-nitroglycals.[15] This methodology affords straightforward and stereoselective access to β-*C*-alkynyl, alkenyl, and alkyl glycosamines and β-*C*-aryl glycosamines as well. At the outset of the project, we attempted the reaction of 2-nitroglucal **1a** with several organometallic derivatives under various conditions (Table 1).

Table 1. Optimization study.[a]



1a **2a**

Entry	M	Solvent	*T* [°C]	Additive	Yield[b] [%]
1	Li	THF	–78 to –40	–	55
2	Li	THF	–78	–	71
3	Li	DME	–78	–	56
4	Li	Et_2O	–78	–	24
5	Li	THF	–78	HMPA[c]	n.r.[d]
6	MgBr	THF	–78	–	n.r.[d]
7	MgBr	THF	0 to r.t.	–	48 (63:37)[e]
8	ZnCl	THF	–78 to r.t.	–	n.r.[d]

[a] Reaction conditions: **1a** (0.16 mmol), C_6H_5–M (0.24 mmol), solvent (2 mL). [b] Yield of isolated product. [c] HMPA = hexamethylphosphoric triamide. [d] n.r.: no reaction. [e] The β/α ratio was determined by ^{1}H NMR spectroscopy.

An initial attempt was performed with phenyllithium as the nucleophile. To our delight, if the reaction was performed at –78 °C and quenched at –40 °C β-arylglycoside **2a** was isolated in 55% yield as a single diastereoisomer (Table 1, entry 1). A slight modification of the reaction quench temperature allowed **2a** to be isolated in 71% yield (Table 1, entry 2). Noteworthy, no formation of the C2 epimer of **2a** was observed, probably because protonation of the latent nitroenolate occurred to deliver the more thermodynamically stable product.[16] Then, a solvent survey revealed that THF was the best solvent; for instance, Et_2O resulted in the isolation of the β isomer in 24% yield. Noteworthy, the addition of HMPA (1.5 equiv.) inhibited the reaction (Table 1, entry 5). Finally, the nature of the organometallic derivative was examined. Interestingly, by using the corresponding Grignard reagent no reaction occurred at –78 °C, whereas the corresponding product was isolated in 48% yield as a 63:37 mixture of β/α adducts if the reaction was performed at 0 °C and allowed to reach room temperature (Table 1, entries 6 and 7). Finally, an organozinc derivative was found to be unreactive in our hands, regardless of the reaction temperature (Table 1, entry 8). Having these optimized conditions in hand, we turned our attention to the scope of the reaction by using 2-nitroglucal **1a** as the substrate and various organolithium derivatives (Table 2).

First, electron-rich aryllithium reagents were engaged under our reaction conditions. Pleasingly, aryllithiums bearing a dioxolane or a methoxy moiety afforded corresponding β adduct **2b** and **2c** in 65 and 67% yield, respectively. Noteworthy, in the case of the methoxy derivative, we were able to isolate 5% of the corresponding α derivative. Then, 4-fluorophenyllithium was tested, which led to the corresponding β-glycoside in modest yield (32%) as a single isomer along with several degradation products. Gratefully, heteroaromatic derivatives reacted smoothly with nitroglucal derivative **1a**. Pyridine derivatives **2e** and **2f** were isolated in good yields of 66 and 45%, respectively, as single diastereoisomers, whereas electron-rich thiophene and furan derivatives gave exclusively β-isomers **2g** and **2h** in 63 and 37% yield, respectively.[17] Then, we turned our attention to the alkynyl and alkenyl derivatives. Pleasingly, the organolithium species derived from phenylacetylene reacted well to provide β-adduct **2i** in 51% yield, whereas lithiated trimethylsilylacetylene afforded β-isomer **2j** in 61% yield along with 18% of the α isomer. Then, vinyllithium and propenyllithium were used to give products **2k** and **2l** in 53 and 65% yield, respectively. In the last case, small quantities of the α-addition product were isolated in 9% yield. Finally, our methodology was extended to aliphatic organolithium species. MeLi was added to glucal **1a** to afford β-isomer **2m** as the sole product in 68% yield. *n*BuLi reacted nicely with **1a** to give β-glycoside **2n** exclusively, whereas $TMSCH_2Li$ furnished corresponding addition product **2o** in 56% yield. In summary, aromatics, heteroaromatics, alkynes, alkenes, and alkyls were all suitable nucleophiles for this transformation, and they gave stereoselectively β-*C*-glucosamines **2a**–**o**.

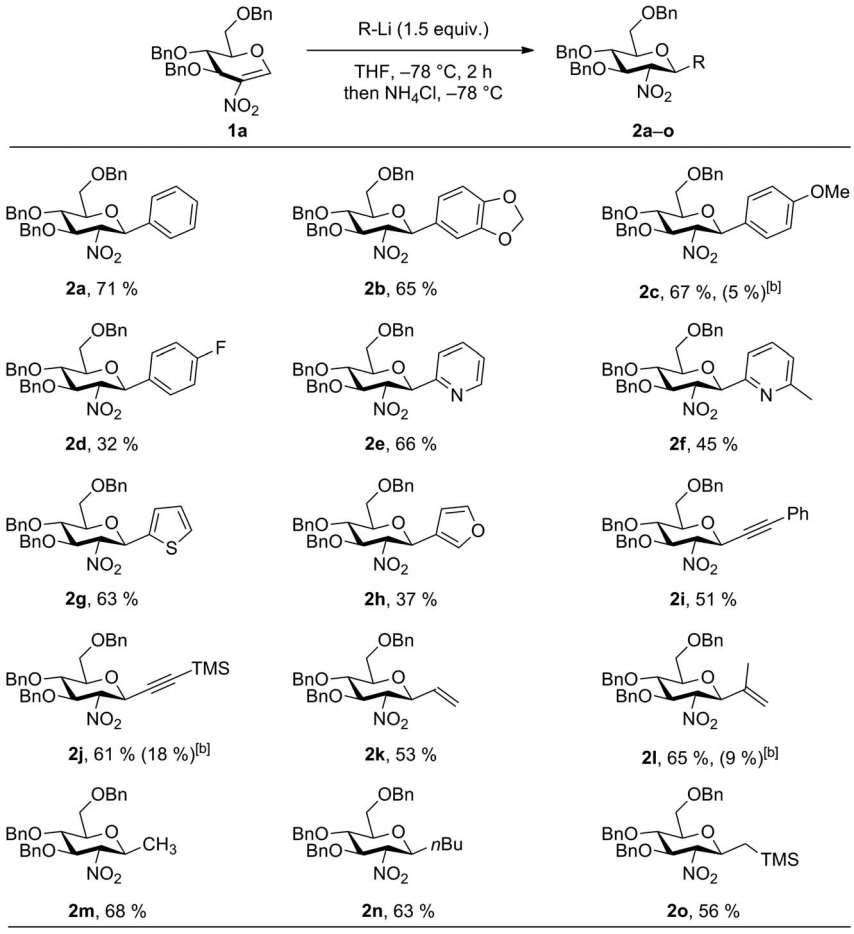
Noteworthy, the stereochemistry of the precursor of the *C*-analogue of glucosamine was determined by ^{1}H NMR spectroscopy experiments (Figure 1).

First, the determination of the coupling constant between H^1 and H^2 (^3J = 9.7 Hz) clearly implied a *trans* relationship, as did the coupling between H^2 and H^3 (^3J = 9.7 Hz). The $^3J(H^3,H^4)$ coupling (^3J = 9.7 Hz) also indicated a *trans* relationship between both protons. Finally, a NOE experiment clearly pointed out a $^4C_1$ conformation of the glycoside, as depicted in Figure 1. Beyond doubt, the β selectivity of the reaction was demonstrated as well as the $^4C_1$ conformation of the addition product.

Then, we checked the efficiency of our methodology on 2-nitroglycals **1b** and **1c** derived from galactal and arabinal, respectively (Table 3).

First, 2-nitrogalactal **1b** was engaged under our reaction conditions with methyllithium as a nucleophile. Pleasingly, product **2ba** was isolated in 75% yield with a 65:35 ratio of the α/β isomers. This lower diastereoselectivity relative to

Table 2. Scope of the reaction.[a]



[a] Reactions conditions: **1a** (0.16 mmol), R–Li (0.24 mmol), THF (2 mL), –78 °C, 2 h, then NH_4Cl. [b] Yield of the isolated α isomer.

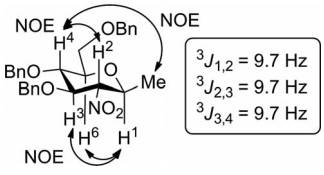
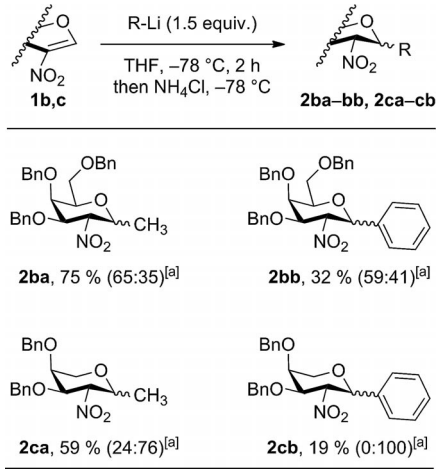


Figure 1. Conformational analysis of **2m**.

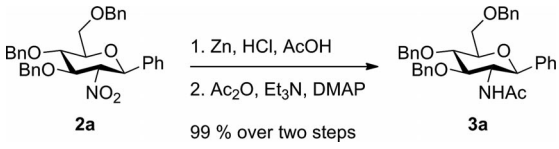
that generally observed with 2-nitroglucal derivatives might be explained by the steric repulsion between the incoming nucleophile and the axial C4 stereogenic center. Thus, we propose that the addition of the lithiated nucleophile should occur either on the less-hindered α side of the $^5H_4$ conformer of **1b** or on the α side of the sterically favored $^4H_5$ conformer. A similar trend was observed with phenyllithium as a nucleophile, and corresponding addition product **2bb** was isolated in 32% yield with poor α/β diastereoselectivity (59:41). Then, we turned our attention to 2-nitroarabinal **1c**. Methyllithium reacted smoothly to give addition product **2ca** in 59% yield with a 76:24 diastereoisomeric ratio (β as a major product). Finally, phenyllithium was used, and β-isomer **2cb** was isolated in 19% yield as a single isomer along with several unidentified byproducts.

Table 3. Extension of the reaction to other glycals.



[a] Ratio of the α and β isomers.

Then, to highlight the versatility of the nitro intermediate, the transformation of nitro derivative **2a** into valuable *N*-acetyl glycoside derivative **3a** was performed (Scheme 2). The reduction of the nitro group to an amine was achieved by using Zn/HCl followed by an acetylation reaction under standard conditions. The resulting *C*–*N*-acetylglycosamine was isolated in quantitative yield over two steps with a single purification step by flash chromatography.



Scheme 2. Access to 1-aryl-2-deoxyaminoglycosides; DMAP = 4-(dimethylamino)pyridine.

Conclusions

In conclusion, we reported stereoselective access to various *C*-glycoside precursors of *C*-glycosamine derivatives. This methodology involving the Michael addition of organolithium derivatives was applied to a broad range of nucleophiles and nitroglycal derivatives. In the case of 2-nitroglucal derivatives, the β stereoisomer was predominantly formed and isolated in good to excellent yields, whereas our process gave moderate selectivities with other 2-nitroglycals, for example, 2-nitrogalactal and 2-nitroarabinal. Finally, we described the easy transformation of this intermediate into the key *C*-glycosamine derivative.

Experimental Section

General Procedure for the Addition to 2-Nitroglycal 1: Under an argon atmosphere, nitroglycal **1** (115 mg, 0.16 mmol, 1 equiv.) was dissolved in dry THF (2 mL), and the solution was stirred at –78 °C. Then, the organometallic derivative (0.24 mmol, 1.5 equiv.) was added over 5 min at –78 °C, and the reaction mixture was stirred at this temperature for 1 h. Then, the resulting mixture was quenched at –78 °C with a solution of NH_4Cl (saturated). The solution was extracted with AcOEt (2× 10 mL). The organic layer was washed with water (1× 10 mL) and brine (1× 10 mL) and dried with $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by preparative TLC (SiO_2, petroleum ether/ethyl acetate).

Supporting Information (see footnote on the first page of this article): Materials and methods, synthesis and characterization, and ^1H NMR and ^{13}C NMR spectra.

Acknowledgments

This work was partially supported by INSA Rouen, Rouen University, Centre National de la Recherche Scientifique (CNRS), European Fund for Regional Development (EFRD) and Labex SynOrg (ANR-11-LABX-0029). T. D. thanks the European Fund for Regional Development (EFRD) (grant number 43209) for a postdoctoral fellowship.

[1] a) R. A. Dwik, *Chem. Rev.* **1996**, *96*, 683–720; b) C. R. Bertozzi, L. L. Kiessling, *Science* **2001**, *291*, 2357–2364.
[2] a) A. Helenius, M. Aebi, *Science* **2011**, *291*, 2364–2369; b) G. W. Hart, M. P. Housley, C. Slawson, *Nature* **2007**, *446*, 1017–1022; c) A. Varki, *Nature* **2007**, *446*, 1023–1029.
[3] For reviews, see: a) P. H. Seeberger, D. B. Werz, *Nature* **2007**, *446*, 1046–1051; b) M. M. Adams, P. Damani, N. R. Perl, A. Won, F. Hong, P. O. Livingston, G. Ragupathi, D. Y. Gin, *J. Am. Chem. Soc.* **2010**, *132*, 1939–1945; c) T. Gilewski, G. Ragupathi, S. Bhuta, L. J. Williams, C. Musselli, X. F. Zhang, K. P. Bencsath, K. S. Panageas, J. Chin, C. A. Hudis, L. Norton, A. N. Houghton, P. O. Livingston, S. J. Danishefsky, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 3270–3275.
[4] For reviews, see: a) J. Stambasky, M. Hocek, P. Kocovsky, *Chem. Rev.* **2009**, *109*, 6729–6764; b) Y. Du, R. J. Linhardt, I. R. Vlahov, *Tetrahedron* **1998**, *54*, 9913–9959; c) P. Sinay, *Pure Appl. Chem.* **1997**, *69*, 459–463; d) P. Sears, C.-H. Wong, *Angew. Chem. Int. Ed.* **1999**, *38*, 2300–2324; *Angew. Chem.* **1999**, *111*, 2446–2471.
[5] Selected examples: a) G. Yang, J. Schmieg, M. Tsuji, R. W. Franck, *Angew. Chem. Int. Ed.* **2004**, *43*, 3818–3822; *Angew. Chem.* **2004**, *116*, 3906–3910; b) S. Xiang, S. Cai, J. Zeng, X.-W. Liu, *Org. Lett.* **2011**, *13*, 4608–4611; c) J. Zeng, S. Vedachalam, S. Xiang, X.-W. Liu, *Org. Lett.* **2011**, *13*, 42–45.
[6] a) M. R. Hansen, L. H. Hurley, *Acc. Chem. Res.* **1996**, *29*, 249–258 and references cited therein; b) T. Bililign, B. R. Griffith, J. S. Thorson, *Nat. Prod. Rep.* **2005**, *22*, 742–760.
[7] a) R. SanMartin, B. Tavassoli, K. E. Walsh, D. S. Walter, T. Gallagher, *Org. Lett.* **2000**, *2*, 4051–4054; b) L. Grant, Y. Liu, K. E. Walsh, D. S. Walter, T. Gallagher, *Org. Lett.* **2002**, *4*, 4623–4625; c) Y. Liu, T. Gallagher, *Org. Lett.* **2004**, *6*, 2445–2448; d) B. A. Roe, C. G. Boojamra, J. L. Griggs, C. R. Bertozzi, *J. Org. Chem.* **1996**, *61*, 6442–6445; e) D. Urban, T. Skrydstrup, J.-M. Beau, *J. Org. Chem.* **1998**, *63*, 2507–2516; f) T. Wakabayashi, M. Shiozaki, S.-I. Kurakata, *Carbohydr. Res.* **2002**, *337*, 97–104; g) J. Cui, D. Horton, *Carbohydr. Res.* **1998**, *309*, 319–330.
[8] a) J. C. Castro-Palomino, R. R. Schmidt, *Liebigs Ann.* **1996**, 1623–1626; b) M. R. E. Aly, R. R. Schmidt, *Eur. J. Org. Chem.* **2005**, 4382–4392; c) T. Kuribayashi, N. Ohkawa, S. Satoh, *Tetrahedron Lett.* **1998**, *39*, 4537–4540.
[9] a) H. Gong, M. R. Gagné, *J. Am. Chem. Soc.* **2008**, *130*, 12177–121183; b) H. Gong, R. S. Andrews, J. L. Zuccarello, S. J. Lee, M. R. Gagné, *Org. Lett.* **2009**, *11*, 879–882.
[10] J. A. C. Romero, S. A. Tabacco, K. A. Woerpel, *J. Am. Chem. Soc.* **2000**, *122*, 168–169, and references cited therein.
[11] For selected examples, see: a) B. G. Reddy, R. R. Schmidt, *Nat. Protoc.* **2008**, *3*, 114–121; b) S. Dharuman, P. Gupta, P. K. Kancharla, Y. D. Vankar, *J. Org. Chem.* **2013**, *78*, 8442–8450; c) G. A. Winterfeld, Y. Ito, T. Ogawa, R. R. Schmidt, *Eur. J. Org. Chem.* **1999**, 1167–1171; d) G. A. Winterfeld, R. R. Schmidt, *Angew. Chem. Int. Ed.* **2001**, *40*, 2654–2657; *Angew. Chem.* **2001**, *113*, 2718–2721; e) W. Xue, J. Sun, B. Yu, *J. Org. Chem.* **2009**, *74*, 5079–5082; f) N. Barroca, R. R. Schmidt, *Org. Lett.* **2004**, *6*, 1551–1554; g) K. Pachamuthu, A. Gupta, J. Das, R. R. Schmidt, Y. D. Vankar, *Eur. J. Org. Chem.* **2002**, 1479–1483; h) G. A. Winterfeld, J. Das, R. R. Schmidt, *Eur. J. Org. Chem.* **2000**, 3047–3050; i) S. Xiang, J. Ma, B. K. Gorityala, X.-W. Liu, *Carbohydr. Res.* **2011**, *346*, 2957–2959; j) B. Bhatt, R. J. Thomson, M. von Itzstein, *J. Org. Chem.* **2011**, *76*, 4099–4104; k) T. Zhang, C.-Y. Yu, Z.-T. Huang, Y.-M. Jia, *Synlett* **2010**, 2174–2178; l) S. Cai, S. Xiang, J. Zeng, B. K. Gorityala, X.-W. Liu, *Chem. Commun.* **2011**, *47*, 8676–8678; m) S. Vedachalam, S. M. Tan, H. P. Teo, S. Cai, X.-W. Liu, *Org. Lett.* **2012**, *14*, 174–177.
[12] B. G. Reddy, Y. D. Vankar, *Angew. Chem. Int. Ed.* **2005**, *44*, 2001–2004; *Angew. Chem.* **2005**, *117*, 2037–2040.
[13] During the preparation of this manuscript, Avenoza and Peregrina reported the addition of an α-selective lithium enolate to

nitro galactals, see: C. Aydillo, C. D. Navo, J. H. Busto, F. Corzana, M. M. Zurbano, A. Avenoza, J. M. Peregrina, *J. Org. Chem.* **2013**, *78*, 10968–10977.
[14] C. W. Holzapfel, C. F. Marais, M. S. van Dyk, *Synth. Commun.* **1988**, *18*, 97–114.
[15] For a similar strategy of Michael addition with organocopper reagents on 2-formylglycals, see: J. Cossy, H. Rakotoarisoa, *Synlett* **2000**, 734–736.
[16] A similar observation was made by Schmidt and co-workers, see ref.[11g]
[17] Several unidentified side products, probably degradation products, were obtained in the crude mixture along with the desired product.

Received: February 1, 2014
Published Online: April 14, 2014

