Tetrahedron Letters 50 (2009) 6484–6487

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Efficient access to disubstituted *exo*-glycals. Application to the preparation of *C*-glycosyl compounds

Alexandre Novoa, Nadia Pellegrini-Moïse *, Sandrine Lamandé-Langle, Yves Chapleur *

Groupe S.U.C.R.E.S., UMR 7565 Nancy Université, CNRS, BP 239, F-54506 Nancy, Vandoeuvre, France

ARTICLE INFO

Article history:
Received 23 July 2009
Revised 28 August 2009
Accepted 2 September 2009
Available online 6 September 2009

Keywords:
Exo-Glycals
Vinylic bromide
Palladium cross-coupling
C-Glycosyl

ABSTRACT

Efficient methods of preparation of disubstituted *exo*-glycals by palladium cross-coupling reaction on the readily available dibromo *exo*-glycal and methoxycarbonyl *exo*-glycal have been developed. Hydrogenation of these new monosubstituted and disubstituted *exo*-glycals proceeded with a high stereocontrol and led to original *C*-glycosyl compounds.

Exo-glycals are olefinic sugars with an exocyclic carbon–carbon double bond at the anomeric centre.[1] Access to these compounds was limited until specific methods were introduced such as the direct olefination of lactones.[2–4] The presence of the ring oxygen strongly influences the reactivity of this double bond, so interesting properties should be expected from these captodative olefins. We have shown that these unique structures are useful precursors of *C*-glycosides by stereoselective reduction of the double bond.[2b,5] Further manipulation of the double bond led to complex *O*-glycoside precursors[6] or to β-amino acids.[7] Several interesting biological properties have been found for *exo*-glycals, triggering our interest to develop synthetic strategies towards these compounds.[8]

Except dihalogeno glycals of type **C** (Fig. 1) that we introduced some years ago,[2] most of the one-step methods for *exo*-glycal formation led to type **A** monosubstituted derivatives (Fig. 1). It would be of interest to reach disubstituted *exo*-glycals of type **B** with, for example, two different substituents or to be able to manipulate readily available *exo*-glycals to build more complex ones by creating carbon–carbon bonds on this olefinic system. If no direct and general solution to the first question has yet been found,[9,4b,h] the second one found an elegant solution in the work of Gomez et al. who reported the manipulation of 1-methylene *exo*-glycals by iodination or bromination providing type **D** *exo*-glycals which were further elaborated to type **A** ones.[10a] Various aryl, heteroaryl, vinyl or alkynyl groups have been introduced stereoselectively and in good yields using Suzuki, Sonogashira and Stille reactions.[10]

The pioneering work of Minato et al. described the stereoselective reaction of 1,1-dichloroalkenes with organometallics in the presence of palladium catalyst.[11] The selectivity, anticipated on the basis of the known rate difference for the palladium cross-couplings of *E*- versus *Z*-1-haloolefins can be efficiently controlled.[12] 1,1-Dihaloolefins have been used in sequential coupling with organozinc,[13a,b,12] organotin,[13c,14] and organoboron[15] reagents and provide a convenient stereospecific route to tri- or tetrasubstituted alkenes.[16]

As type **C** dihaloolefins are readily available in one step and in excellent yields from lactones, we decided to explore the reactivity of these compounds in palladium-catalyzed carbon–carbon bond formation. Furthermore, as type **A**, methoxycarbonyl *exo*-glycal also readily available from lactone has been brominated and the reactivity of the corresponding vinylic bromoester has been investigated in palladium-catalyzed cross-coupling reactions. The access to *C*-glycosides by reduction of the exocyclic double bond has been explored. We report in this letter the results of this study.

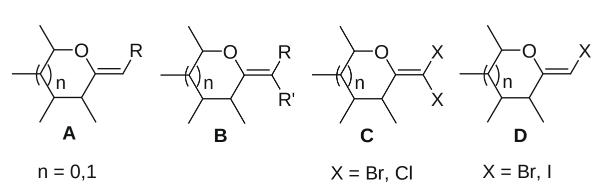


Figure 1. Different types of substituted *exo*-glycals.

* Corresponding authors.
E-mail addresses: Nadia.Pellegrini@sucres.uhp-nancy.fr (N. Pellegrini-Moïse), Yves.Chapleur@sucres.uhp-nancy.fr (Y. Chapleur).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.09.019

Type **C** dichloroolefins are poorly reactive and did not suffer modifications of the carbon chlorine bond except reduction. Thus we turned to the dibromo *exo*-glycal **1,** prepared from the corresponding protected D-gulono-γ-lactone as a model compound. The key point would be the selectivity of the cross-coupling reaction because of a likely difference in the reactivity of the two bromine atoms of **1**. Two types of palladium-catalyzed cross-coupling reaction have been investigated. Indeed, three possible compounds can be obtained: **2** and **3** resulting from the replacement of (*E*) and (*Z*)-bromine atoms, respectively, and the disubstituted *exo*-glycal **4** obtained by subsequent coupling of **2** and/or **3** (Scheme 1).

The Suzuki reaction was investigated first with five different boronic acids as coupling partners (Table 1).[17] $Pd(Ph_3)_4$ was first investigated to perform the cross-coupling reaction: disubstituted *exo*-glycals **4** were major products in most of the cases and some starting material was recovered. A series of experiments was performed to find the best experimental conditions and in every case, compound **2** as (*Z*)-isomer became the major product. The soft ligand trifurylphosphine (TFP) was used in 30 mol % with $Pd_2(dba)_3$ and $PdCl_2(PPh_3)_2$. The combination of TFP/$PdCl_2(PPh_3)_2$ appeared to be the best coupling conditions with excellent conversion rates leading to a good to excellent stereoselectivity. The palladium-catalyzed reaction of the dibromo *exo*-glycal first took place at the trans carbon–halogen bond, meaning that the first oxidative addition always takes place on the less crowded carbon–bromine bond. Only the major product **2** was isolated as a pure compound by column chromatography, the other products being difficult to separate from each other. Monosubstituted isomers were formed with good to excellent ratio in favour of compounds **2a**–**e**. Only small amounts of (*E*)-isomers **3** and biscoupled compounds **4** were formed and some starting material was recovered. The use of microwave activation (CEM Discover®) to perform this Suzuki cross-coupling reaction did not improve the yields and the stereoselectivity of the reaction. A second series of experiments was performed on dibromo *exo*-glycal **1** using Stille cross-coupling conditions (Scheme 1, Table 1). The Stille reaction has gained wide acceptance in synthetic organic chemistry thanks to the availability of organostannanes, the mild reaction conditions being compatible with many functional groups.[18]

It allows for example the introduction of methyl-acrylate, 2-phenylethenyl and 2-(trimethylsilyl)ethenyl groups prepared by hydrostannylation of the corresponding alkyne. All reactions were carried out in toluene with TFP (30 mol %) with 5 mol % of $Pd_2(dba)_3$ palladium catalyst. As observed with Suzuki cross-coupling, the (*Z*)-isomer **2** was always the major product. Performing the reactions under microwave irradiations led to higher stereoselectivity and to better yields of pure compound **2**, as compared to thermal activation. The 2-thienyl and phenyltributyl stannane couplings gave selectivities comparable with Suzuki cross-coupling (see entries 1 and 2, 4 and 5). It is noteworthy that the (*Z*)-isomer **2a** was obtained in better yield with Suzuki cross-coupling reaction. An excellent stereoselectivity was observed using methyl (*E*)-tributylstannyl acrylate, and **2f** was formed with an excellent (*Z*)/(*E*) ratio (entry 8).

Microwave activation led to monosubstituted (*Z*)-isomers **2g** and **2h** in excellent ratio (entries 9 and 10) as shown by ^{1}H NMR, but these compounds proved unstable and decomposed on silica gel even if neutralized with base.

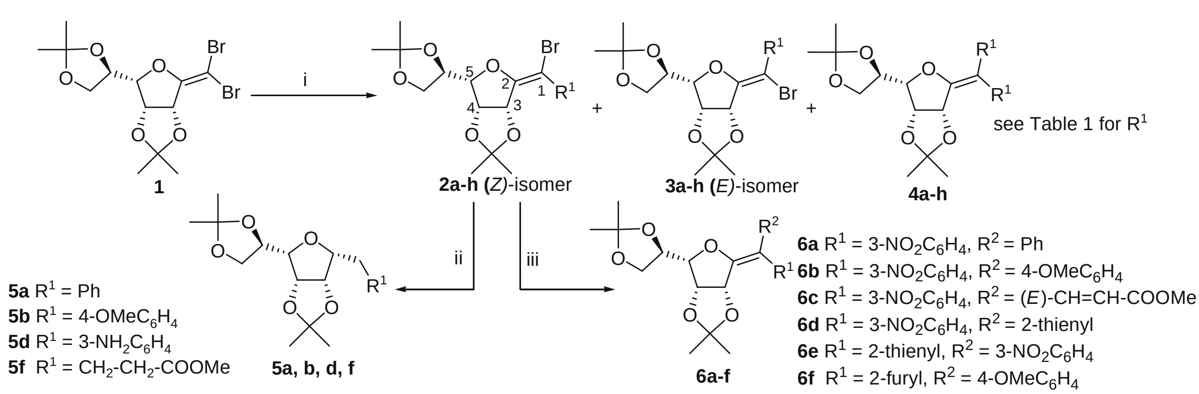
The stereochemistry of major isomer **2a** was unambiguously confirmed as (*Z*) by single-crystal X-ray analysis. On this compound, NOE difference spectroscopy showed a strong interaction between H-3 and two aromatic protons whereas no significant correlation was observed for the minor (*E*)-isomer **3a**, confirming a (*Z*)-geometry of **2a**. Moreover in the ^{1}H NMR spectrum, the H-3 signal appears upfield for (*Z*)-isomer **2a** (4.98 ppm) as compared to (*E*)-isomer **3a** (5.52 ppm). This chemical shift difference was used to assign the (*Z*)-configuration of substituted *exo*-glycals **2b**–**h**.

C-Glycosyl compound formation is a useful application of *exo*-glycals.[19,2b,5] Double bond reduction proceeds with high stereocontrol due to the strong directing effect of the acetal group on the sugar template. Reductive hydrogenation of monosubstituted

Table 1
Palladium cross-coupling reactions on dibromo *exo*-glycal

Entry	$R^1B(OH)_2$ or R^3SnBu_3	Ratio[a] **2**/**3**/**4**	Yields[b] of **2**
1	$PhB(OH)_2$	1/0/1	**2a**—60
2	$PhSnBu_3$	2/1/0	**2a**—33
3	4-$OMeC_6H_4B(OH)_2$	5/1/1	**2b**—62
4	2-Thienyl-$B(OH)_2$	4/1/0	**2c**—60
5	2-Thienyl-$SnBu_3$	2/1/1	**2c**—60
6	3-$NO_2C_6H_4B(OH)_2$	6/1/2	**2d**—61
7	2-Furyl-$B(OH)_2$	9/0/1	**2e**—60
8	(*E*)-MeOOC–CH=CH–$SnBu_3$	7/1/1	**2f**—60
9	(*E*)-Me_3Si–CH=CH–$SnBu_3$	10/1/3	**2g**[c]
10	(*E*)-Ph–CH=CH–$SnBu_3$	10/1/3	**2h**[c]

[a] Estimated by ^{1}H NMR on H-3 chemical shift.
[b] Yields after purification.
[c] Decomposed on column chromatography.



Scheme 1. Palladium-catalyzed cross-coupling reactions on dibromo *exo*-glycal **1** and hydrogenation. Reagents and conditions: (i) Suzuki cross-coupling: $R^1B(OH)_2$ (1.5 or 2 equiv), DME, K_2CO_3 2 M (2 equiv/equiv boronic acid), $PdCl_2(PPh_3)_2$ (5 mol %), TFP (30 mol %), 85 °C, 24 h or Stille cross-coupling: R^1SnBu_3 (1.5 equiv), toluene, $Pd_2(dba)_3$ (5 mol %), TFP (30 mol %), 140 °C, microwave irradiation in a sealed tube, 45 min; (ii) H_2, 10 bars, Ni Raney, EtOAc, rt; (iii) Suzuki cross-coupling: $R^2B(OH)_2$ (2 equiv), DME, K_2CO_3 2 M (4 equiv), $Pd(PPh_3)_4$ (5 mol %), 85 °C, 24 h, or Stille cross-coupling: R^2SnBu_3 (2 equiv), toluene, Pd_2dba_3 (5 mol %), TFP (30 mol %), 140 °C, microwave irradiation in a sealed tube, 45 min.

Table 2
Disubstituted *exo*-glycals by sequential cross-coupling

Entry	Starting *exo*-glycals	$R^2B(OH)_2$ or R^2SnBu_3	Compounds/yields[a]
1	**2d**	$PhB(OH)_2$	**6a**/85
2	**2d**	$4\text{-}OMeC_6H_4B(OH)_2$	**6b**/95
3	**2d**	(*E*)-MeOOC–CH=CH–$SnBu_3$	**6c**/66
4	**2d**	2-Thienyl-$B(OH)_2$	**6d**/60
5	**2c**	$3\text{-}NO_2C_6H_4B(OH)_2$	**6e**/85
6	**2e**	$4\text{-}OMeC_6H_4B(OH)_2$	**6f**/85

[a] Yields after purification.

Table 3
Palladium cross-coupling reaction and hydrogenation of **8**

Entry	R^3	Compounds/yields[a]	Compounds/yields[a]
1	$3\text{-}NO_2C_6H_4$	**9a**/68	**10a**/54
2	$4\text{-}OMeC_6H_4$	**9b**/64	–
3	2-Naphthyl	**9c**/81	**10c**/40

[a] Yields after purification.

exo-glycals **2** in ethyl acetate over Raney nickel gave compounds **5** as single isomers in good to excellent yields (88% for **5a**, 77% for **5b**, 46% for **5d** and 69% for **5f**) (Scheme 1). As expected, the *C*-glycosyl chain lies on the α face as shown by the proton coupling constants. Hydrogenation of bromo *exo*-glycals **2c** and **2e** bearing a thienyl and furyl group, respectively, failed under these conditions and decomposition took place.

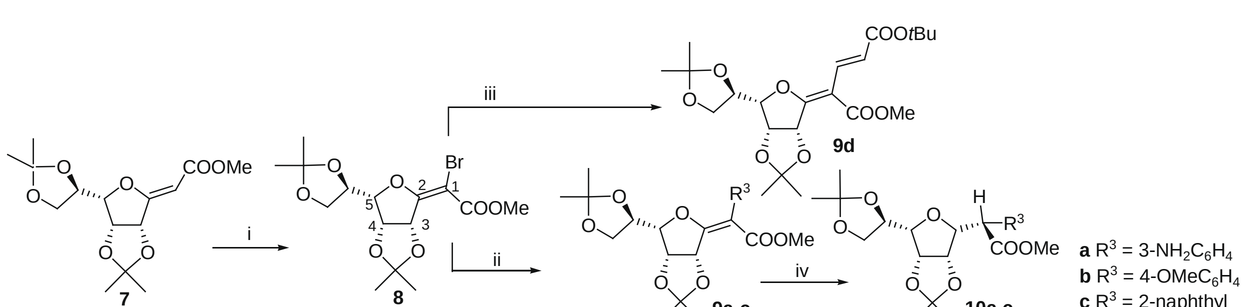
Having developed efficient methods for stereoselective monosubstitution of the dibromo *exo*-glycal **1**, we focused our attention on the substitution of the remaining bromine atom in a palladium cross-coupling reaction, allowing the access to disubstituted *exo*-glycals (Scheme 1). This sequential cross-coupling allowed us to obtain aromatic or heteroaromatic and ethylenic *exo*-glycals. All disubstituted compounds **6** have been obtained in excellent yields (Table 2). This approach is highly versatile, since any stereoisomer can be synthesized in a stereochemically pure form by simply modifying the order of the reagents. This was illustrated on one example using 2-thienyl and 3-nitrophenyl boronic acids (entries 4 and 5). All attempts (Pd/C, Ni Raney, PtO_2 under mild or high pressure) to reduce the *exo*-glycals **6** failed.

Given the straightforward carbon–carbon bond formation on dihalogenated *exo*-glycals, we sought a more functionalized monobromo *exo*-glycal. Thus we investigated the bromination of the double bond of the known *exo*-glycal **7** (Scheme 2).[3] No bromination occurred on treatment of both isomers with NBS in chlorinated solvents.[20] In contrast, treatment of the (*Z*) unsaturated ester **7** with Br_2 followed by hydrogen bromide elimination in the presence of NEt_3 in CH_2Cl_2 or better in CCl_4 gave the expected α-brominated compound in 50% yield as a 8:2 *Z*/*E* mixture which were separated by chromatography, 45% of the starting material being recovered. Attempts to improve the conversion rate of the starting material by using excess of Br_2 higher temperature were unsuccessful. It is worth noting that the (*E*)-isomer did not suffer bromination whatever the conditions used. The double bond configuration of the major compound **8** was assigned as (*Z*) on the basis of NMR spectral data. The H-3 signal appears upfield for (*E*)-isomer (5.39 ppm) as compared to (*Z*)-isomer (5.79 ppm) due to the presence of methoxycarbonyl function.[3]

The palladium-catalyzed cross-coupling reactions of the pure (*Z*)-*exo*-glycal **8**, formed predominantly, were next investigated (Scheme 2, Table 3). The Suzuki cross-coupling was carried out in refluxing 1,4-dioxane for 24 h. The resulting disubstituted *exo*-glycals **9** were obtained in good yields. For compound **9a**, NOE difference spectroscopy showed an interaction between H-3 and the methoxy group of the ester function and no interaction between H-3 and aromatic protons, supporting the stereochemistry depicted in Scheme 2. Attempted Stille cross-coupling reactions on bromo-*exo*-glycal **8** remained unsuccessful. However, the coupling of **8** with *tert*-butyl acrylate led to compound **9d** in 58% yield, indicating the potential of functionalization by the Heck reaction.

While hydrogenation reaction of disubstituted *exo*-glycals **6** described above failed, the hydrogenation of disubstituted *exo*-glycals **9a** and **9c** bearing an ester function was successfully accomplished in ethyl acetate using PtO_2 as the catalyst (Scheme 2). Here again, the double bond reduction proceeded with high stereocontrol, compounds **10** being obtained as single isomers in good yields. Given the (*E*)-geometry of the double bond in compounds **9**, the corresponding reduced compounds **10** were obtained with an (*S*)-configuration at the newly created asymmetric centre.

Efficient methods of substitution of the readily available dibromo *exo*-glycal **1** by sequential palladium-catalyzed cross-coupling reaction has been developed and led to disubstituted original *exo*-glycals as single stereoisomers. The readily accessible *exo*-glycal **7** has been successfully brominated and the resulting vinylic bromide was functionalized by Suzuki and Heck cross-coupling reaction. Hydrogenation of monosubstituted and disubstituted *exo*-glycals bearing an ester function proceeded with a high stereocontrol and led to original *C*-glycosyl compounds, creating a new chiral centre for some of them. The application of this methodology for the synthesis of biologically relevant *C*-glycosyl compounds is under active investigation.



Scheme 2. Bromination, functionalization and hydrogenation of *exo*-glycal **7**. Reagents and conditions: (i) Br_2 (1.1 equiv), NEt_3 (1.1 equiv), CCl_4, 0 °C to rt, 24 h; (ii) $R^3B(OH)_2$ (2 equiv), $PdP(Ph_3)_4$, K_2CO_3 (2 M), 1,4-dioxane, 110 °C, 24 h; (iii) CH_2=CH–COO*t*Bu (2 equiv), $PdP(Ph_3)_4$, NEt_3, DMF, 120 °C, 24 h; (iv) H_2, 45 bars, PtO_2, EtOAc, rt, 24 h.

Acknowledgements

We thank Dr. F. Chrétien for helpful discussions, and B. Fernette, F. Dupire, S. Adach for technical assistance.

Supplementary data

Supplementary data (experimental procedures, characterizations and X-ray analysis of **2a**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.019.

References and notes

1. Taillefumier, C.; Chapleur, Y. *Chem. Rev.* **2004**, *104*, 263–292.
2. (a) Chapleur, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 449; (b) Bandzouzi, A.; Chapleur, Y. *Carbohydr. Res.* **1987**, *171*, 13–23; (c) Lakhrissi, M.; Chapleur, Y. *Synlett* **1991**, 583–587; (d) Lakhrissi, M.; Chapleur, Y. *J. Org. Chem.* **1994**, *59*, 5752–5757; (e) Lakhrissi, Y.; Taillefumier, C.; Chrétien, F.; Chapleur, Y. *Tetrahedron Lett.* **2001**, *42*, 7265–7268.
3. Lakhrissi, M.; Chapleur, Y. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 750–752.
4. For stepwise olefinations see: (a) Molas, P.; Matheu, M. I.; Castillon, S. *Tetrahedron Lett.* **2004**, *45*, 3721–3724; (b) Gueyrard, D.; Haddoub, R.; Salem, A.; Bacar, N. S.; Goekjian, P. G. *Synlett* **2005**, 520–522; (c) Xu, M.; Miao, Z.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **2005**, *88*, 2918–2937; (d) Miao, Z.; Xu, M.; Hoffmann, B.; Bernet, B.; Vasella, A. *Helv. Chim. Acta* **2005**, *88*, 1885–1912; (e) Taylor, R. J. K.; McAllister, G. D.; Franck, R. W. *Carbohydr. Res.* **2006**, *341*, 1298–1311; (f) Yamanoi, T.; Nara, Y.; Matsuda, S.; Oda, Y.; Yoshida, A.; Katsuraya, K.; Watanabe, M. *Synlett* **2007**, 785–789; (g) Zhu, X. M.; Jin, Y.; Wickham, J. *J. Org. Chem.* **2007**, *72*, 2670–2673; (h) Bourdon, B.; Corbet, M.; Fontaine, P.; Goekjian, P. G.; Gueyrard, D. *Tetrahedron Lett.* **2008**, *49*, 747–749.
5. Lakhrissi, Y.; Taillefumier, C.; Lakhrissi, M.; Chapleur, Y. *Tetrahedron: Asymmetry* **2000**, *11*, 417–421.
6. (a) Lin, C.-H.; Lin, H.-C.; Yang, W.-B. *Curr. Top. Med. Chem.* **2005**, *5*, 1431–1457; (b) Hsu, S.-J.; Lin, H.-C.; Lin, C.-H. *Carbohydr. Res.* **2006**, *341*, 1428–1437.
7. (a) Taillefumier, C.; Lakhrissi, Y.; Lakhrissi, M.; Chapleur, Y. *Tetrahedron: Asymmetry* **2002**, *13*, 1707–1711; (b) Andreini, M.; Taillefumier, C.; Fernette, B.; Chapleur, Y. *Lett. Org. Chem.* **2008**, *5*, 360–364.
8. (a) Caravano, A.; Vincent, S. P.; Sinay, P. *Chem. Commun.* **2004**, 1216–1217; (b) Stolz, F.; Reiner, M.; Blume, A.; Reutter, W.; Schmidt, R. R. *J. Org. Chem.* **2004**, *69*, 665–679; (c) Caravano, A.; Dohi, H.; Sinay, P.; Vincent, S. P. *Chem. Eur. J.* **2006**, *12*, 3114–3123.
9. For some examples see: (a) Hall, R. H.; Bischofberger, K.; Eitelman, S. J.; Jordaan, A. J. *Chem. Soc., Perkin Trans. 1* **1977**, 2236–2241; (b) Lamberth, C. *Carbohydr. Lett.* **1999**, *3*, 375–380.
10. (a) Gomez, A. M.; Pedregosa, A.; Valverde, S.; Lopez, J. C. *Tetrahedron Lett.* **2003**, *44*, 6111–6116; (b) Gomez, A. M.; Danelon, G. O.; Pedregosa, A.; Valverde, S.; Lopez, J. C. *Chem. Commun.* **2002**, 2024–2025; (c) Gomez, A. M.; Pedregosa, A.; Barrio, A.; Valverde, S.; Lopez, J. C. *Tetrahedron Lett.* **2004**, *45*, 6307–6310; (d) Gomez, A. M.; Barrio, A.; Amurrio, I.; Valverde, S.; Jarosz, S.; Lopez, J. C. *Tetrahedron Lett.* **2006**, *47*, 624–6246; (e) Li, X.-L.; Xu, X.-M.; Tian, J.; Li, Y.-X. *Chin. J. Chem.* **2005**, *23*, 1564–1568.
11. Minato, A.; Suzuki, K.; Tamao, K. *J. Am. Chem. Soc.* **1987**, *109*, 1257–1258.
12. Tan, Z.; Negishi, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 762–765.
13. (a) Shi, J.-c.; Zeng, X.; Negishi, E.-i. *Org. Lett.* **2003**, *5*, 1825–1828; (b) Zeng, X.; Qian, M.; Hu, Q.; Negishi, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 2259–2263; (c) Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873–8879.
14. (a) Shen, W. *Synlett* **2000**, 737–739; (b) Sorg, A.; Siegel, K.; Brückner, R. *Synlett* **2004**, *2004*, 321–325.
15. (a) Roush, W. R.; Riva, R. *J. Org. Chem.* **1988**, *53*, 710–712; (b) Alvarez, R.; Iglesias, B.; De Lera, A. R. *Tetrahedron* **1999**, *55*, 13779–13790; (c) Evans, D. A.; Starr, J. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1787–1790; (d) Molander, G. A.; Yokoyama, Y. *J. Org. Chem.* **2006**, *71*, 2493–2498; (e) Takeda, Y.; Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 8659–8661.
16. For reviews see: (a) Sugihara, T. In *Palladium-catalyzed cross-coupling with other alpha-hetero-substituted organic electrophiles*; Negishi, E.-i., Ed.; Handbook of Organopalladium Chemistry for Organic Synthesis; Wiley-Interscience, 2002; Vol. 1, pp 649–655; (b) Reiser, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 2838–2840.
17. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
18. (a) Stille, J. K. *Angew. Chem., Int. Ed.* **1986**, *98*, 508–524; (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1–652.
19. Bandzouzi, A.; Chapleur, Y. *J. Chem. Soc., Perkin Trans. 1* **1987**, 661–664.
20. (a) Bellur, E.; Langer, P. *Eur. J. Org. Chem.* **2005**, 4815–4828; (b) Bellur, E.; Langer, P. *J. Org. Chem.* **2005**, *70*, 7686–7693.