CHEMISTRY
AN ASIAN JOURNAL
www.chemasianj.org

Accepted Article

Title: Controllable activation of Pd-G3 palladacycle precatalyst in the presence of thiosugars: rapid access to 1-aminobiphenyl thioglycoside atropoisomers at room temperature

Authors: Samir Messaoudi, Riyadh Ahmed Atto Al-Shuaeeb, Mouad Alami, and Camille Dejean

To be cited as: *Chem. Asian J.* 10.1002/asia.201701415

Link to VoR: http://dx.doi.org/10.1002/asia.201701415

A Journal of
ACES Asian Chemical Editorial Society

A sister journal of Angewandte Chemie and Chemistry – A European Journal

WILEY-VCH

10.1002/asia.201701415

WILEY-VCH

Controllable activation of Pd-G3 palladacycle precatalyst in the presence of thiosugars: rapid access to 1-aminobiphenyl thioglycoside atropoisomers at room temperature

Riyadh Ahmed Atto AL-Shuaeeb,[a] Camille Dejean,[a] Mouâd Alami,*[a] and Samir Messaoudi*[a]

Abstract: A controllable method for the functionalization of XantPhos Pd-G3 precatalyst with thiosugars and thiols has been established. Under mild and operationally simple reaction conditions through just mixing of precatalyst and thiosugars (α- or β-mono-, di- and poly-thiosugar derivatives) in water at 25 °C for 20 min, a series of 1-aminobiphenyl thioglycosides that are difficult to synthesize by classical methods, has been synthesized in very high yields.

The biaryl motif is a fundamental core component and constitutes an important class of compounds that find widespread use as pharmaceuticals,[1] natural products,[2] ligands[3], catalysts[3] and in material industries.[4] As depicted in the Figure 1, the biaryl core represents the principle architecture in various top marketed drugs such as the antihypertensives valsartan and telmisartan as well as the non-steroidal anti-inflammatory drug diflunisal. 2-Aminobiphenyls are one of the most important subdivisions of functionalized biaryls primarily found in biologically active natural products and pharmaceuticals[5] such as the agrochemical agent boscalid and the natural product ambidalmine (Figure 1). Furthermore, a wide variety of chiral ligands and catalysts based on the biaryl scaffolds such as 2-aminobinaphtyl NOBIN were utilized in numerous asymmetric transformations to produce important chiral compounds in optically enriched form.[6] Besides all these utilities, 2-aminobiphenyls are used as pivotal key intermediates to access functionalized heterocycles such as carbazoles,[7] phenanthridinones,[8] phenanthrenes[9] and dibenzofurans.[10] The most direct method used for the synthesis

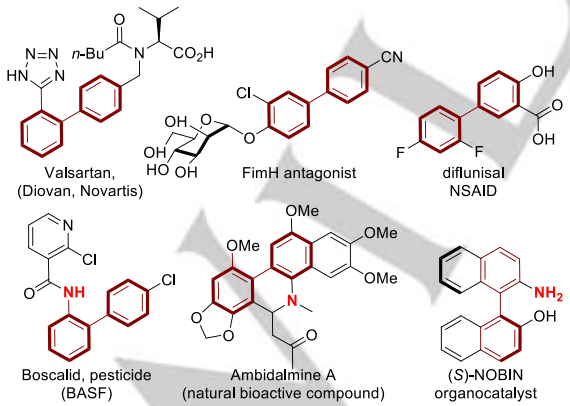


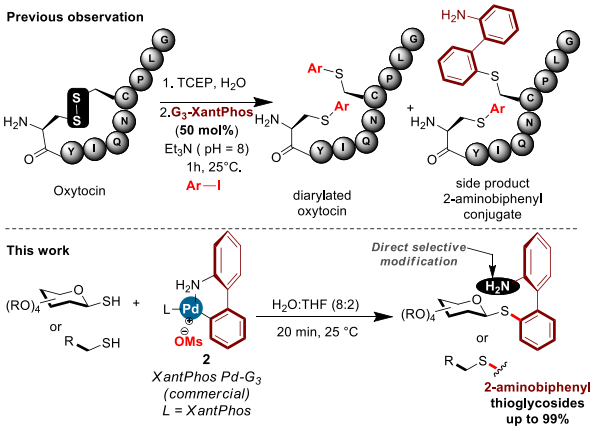
Figure 1. Examples of some useful molecules containing the biaryl core

[a] Dr.RAA AL Shuaeeb, C. Dejean, Dr. M. Alami, Dr. S. Messaoudi, BioCIS, Univ. Paris-Sud, CNRS, University Paris-Saclay, Châtenay-Malabry, France Tel: + (33) 0146835887; E-mail: samir.messaoudi@u-psud.fr,

Supporting information for this article are available on the www

of functionalized 2-aminobiphenyls is Suzuki–Miyaura cross-coupling of haloanilines with boronic acid derivatives. Surprisingly, a thorough literature search revealed a lack of methods to access substituted 2-aminobiphenyls bearing polyfunctionnal complex groups such as sugar moieties. Owing to the significance importance of 2-aminobiphenyls there is a strong impetus to discover new chemical transformations for their efficient synthesis and functionalization.

We recently reported an efficient protocol for the bioconjugation of cysteine-containing peptides through the use of the palladacycle pre-catalyst Xantphos Pd-G3.[11] When the therapeutic peptide oxytocin was used as a substrate (Scheme 1), the disulfide bridge of the peptide was reduced and the two *in situ* generated thiols reacted with iodoarenes, in the presence of G3-XantPhos (50 mol%). Under these conditions, the diarylated oxytocin was formed as the major product together with a by-product, which corresponds to the mixed naphthalene/2-aminobiphenyl conjugate (m/z = 1302.4), arising from the reaction of the thiol function of cysteine with the Pd-G3-precatalyst (Scheme 1). This by-product, although obtained in a traces amount, pointed to the principal feasibility of this alluring reaction of Pd-G3-precatalyst with thiols into a 2'-*S*-linked 2-aminobiphenyls under mild reaction conditions (Scheme 1). Thus, we envisioned in the present study whether XantPhos Pd-G3 precatalyst could be reacted with various thiol derivatives such as 1-thiosugars to synthesize a range of 2-*S*-glycosylated-2'-aminobiphenyls (Scheme 1). If further developed, such a transformation could provide an easy and very fast access to substituted 2-aminobiphenyl under mild (25 °C) and operationally simple reaction conditions. Continuing our efforts to provide the community of chemists with more efficient ways to produce high value thioglycosides,[12] we describe herein how this controlled

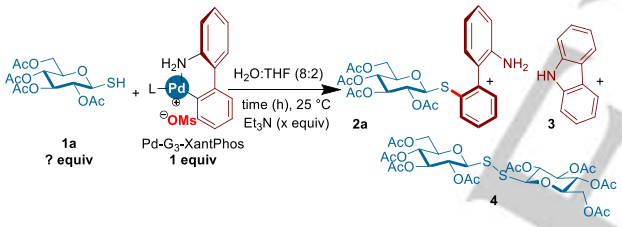


Scheme 1 previous observations and present work process can be used as a step-efficient and modular method to synthesize 2'-glycosyl-2-aminobiaryls.

10.1002/asia.201701415

To verify the proposed strategy, our initial investigation focused on identifying optimal conditions for the functionalization of XantPhos Pd-G3 palladacycle precatalyst with the tetra-*O*-acetylated 1-thio-β-D-glucopyranose **1a** in the presence of Et_3N (1.2 equiv), in H_2O/THF combination ([0.1 M]). Thus, reaction of **1a** with XantPhos Pd-G3 in the presence of Et_3N (1.2 equiv) in H_2O:THF (8:2, v/v) for 2 h at room temperature led to complete conversion of the precatalyst into the carbazole **3** together with sugar disulfide **4** but the desired compound **2a** was not detected (Table 1, entry 1). This result is not surprising since the activation of the precatalyst in the presence of Et_3N is well known.[13] To overcome the formation of this undesired carbazole **3**, we conducted the model reaction in the presence of 0.5 equivalents of Et_3N. Under these conditions compound **2a** was isolated in an acceptable 56% yield together with the carbazole **3** and the disulfide **4** (entry 2). Delightfully, when the reaction was performed in the absence of the base, using otherwise identical conditions, the conversion rate of the precatalyst is total and the activation is selective toward the desired aminobiphenyl thioglycoside **2a** (99% yield, entry 3). Shortening the reaction time until 20 min led to same yield (entry 4). Thus, the best conditions were found to require **1a** (2 equiv) and XantPhos Pd-G3 (1 equiv) in H_2O:THF (8:2) stirring for 20 min at 25 °C. Under these conditions, **2a** was isolated in a 99% yield.

Table 1: Survey of reaction conditions for the coupling of XantPhos Pd-G3 with the *tetra*-*O*-acetylated 1-thio-b-D-glucopyranose **1a**[a]



entry	Et_3N (equiv)	equiv of **1a**	t (h)	% yield (**2a**)[b]
1	1.2	1.5	1	0[c]
2	0.5	1.5	1	56[d]
3	-	2	1	99
4	**-**	**2**	**0.3**	**99**
5	**-**	**2**	**0.3**	**99**[e]

[a] **1a** (x equiv), XantPhos Pd-G3 (1 equiv), in H_2O: THF (8:2, v/v) [0.1M]) at 25 °C. [b] Yield of the isolated product **2a**. [c] Compound **2a** was not detected and only the formation of carbazole **3** together with sugar disulfide **4** were observed. [d] Carbazole **3** together with sugar disulfide **4** were also isolated. [e] Reaction was performed in only THF

The structure of the product **2a** was unambiguously determined by ^1H and ^{13}C NMR as well as 2D experiments. Interestingly, ^1H- and ^{13}C-NMR analysis showed the presence of doubling signals in the whole spectrum. As we can see in Figure 2A, the signals of the acetate groups at 2.1-1.8 Hz are doubled to eight singlets (8 x CH_3) with identical integrals length. This result demonstrates the presence of two diastereoisomers in a 1:1 ratio (Figure2A). The origin of signal doubling was investigated and the coalescence temperature of **2a** has been determined using variable-temperature (VT) ^1H-NMR studies (Figure 2B). A single sharp signal was detectable at around 5.05 ppm, however as the temperature is lowered, the signal broadens and ultimately splits into two peaks around the critical coalescence temperature of 280 K. These data confirmed the hypothesis that the doubling of signals in the ^1H- and ^{13}C-NMR spectra at 280 K (coalescence temperature) was due to the presence of two atropoisomers of 2-aminobiphenyl **2a** in 1:1 ratio separated by a relative energy barrier of $DG^{\#}$(280 K) = 14.49 kcal/mol.[14]

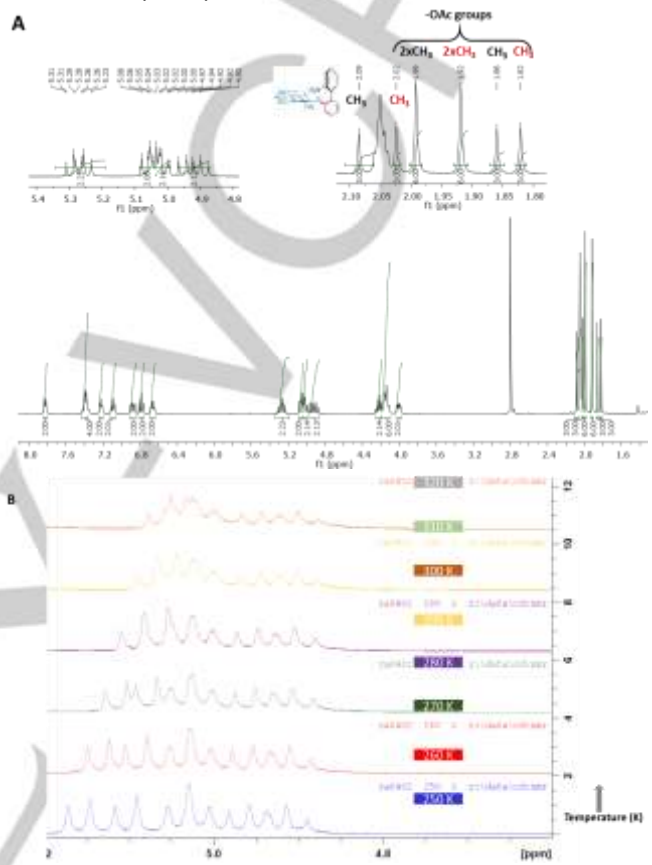
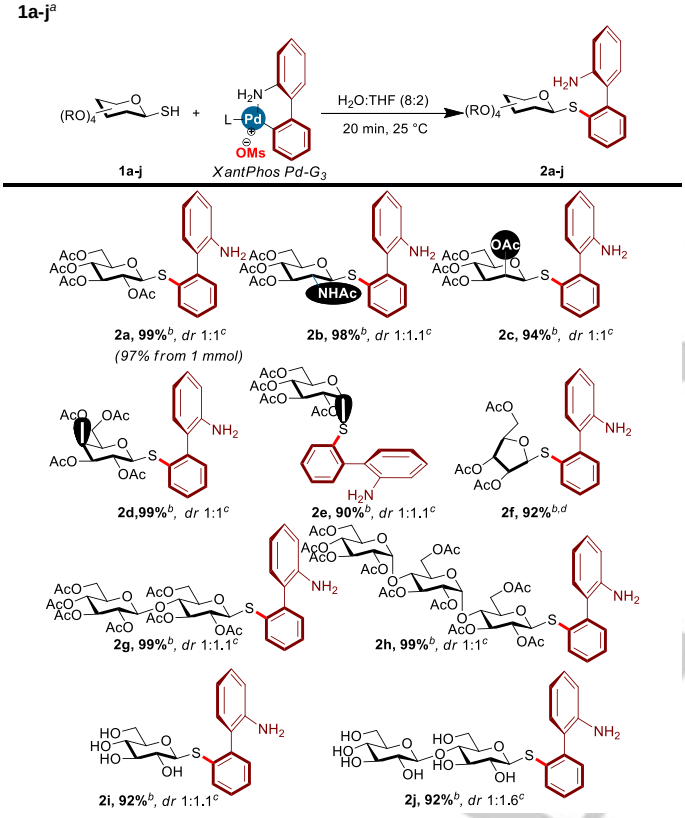


Figure 2. (**A**) ^1H-NMR of **2a**. (**B**) Variable-temperature (VT) ^1H-NMR studies

Motivated by these results, we next explored the scope of the coupling of structurally diverse α- or β-mono-, di- and poly-thiosugar derivatives with XantPhos Pd-G3 (Scheme 2). Gratifyingly, all the couplings proceeded in excellent yields and tolerate a large variety of thiosugars **1a-i** with a perfect retention of the anomeric configuration. *O*-acetylated 1-thio- β-D-glycopyranose **1a**, *O*-acetylated *N*-Ac-1-thio- β-D-glucopyranose **1b**, *O*-acetylated 1-thio- β-D-galactopyranose **1c** and *O*-acetylated 1-thio- β-D-mannocopyranose **1d** were reacted selectively with XantPhos Pd-G3 to furnish saccharides **2a-d** without any loss of reactivity. Importantly, this procedure is not limited to only β-glycosyl thiols, but it also worked successfully with 1-thioglucose **1e**, which had an anomeric α-configuration. In this case, the corresponding α-saccharide product **2e** was obtained with a slightly lower yield of 90% and 1.1:1 atropodiastereomeric ratio. Thus, the activation of XantPhos Pd-G3 by α-thioglucose **1e** induces atropo diastereoselectivity during the activation process. Additionally, the coupling also works with the challenging 1-thio– β-D-ribose partner, furnishing **2f** in an excellent 90% yield. Moreover, the reaction is not limited

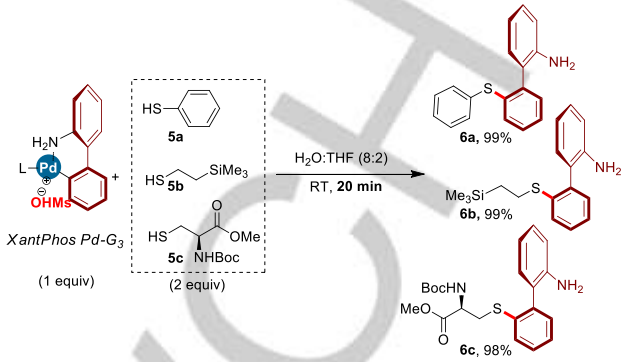
to only monosaccharides, but can be applied in the cases of more complex di- and trisaccharide derivatives. Thus, 1-thio- β-D-cellobiose **1g** as well as 1-thio- β-D-maltotriose **1h** were efficiently reacted with Pd-G3 precatalyst to give the corresponding 2-aminobiphenyl β-thioglycosides **2g-i** in quantitative yields. Importantly, the stereochemistry of the β-1,4'-*O*-glycosidic bond in the tri-saccharides **2g,h** and the α-1,4' in β-tri- saccharide **2h** remained intact. Importantly, there is no significant impact of protecting groups on the reactivity of the glycosyl thiols derivatives since unprotected thiosugars **1i**,**j** react similarly as their *O*-acetated congeners furnishing the 2-aminobiphenyl β-thioglycoside atropodiastereomers **2i** and **2j** in excellent yields and an atropodiastereomeric ratios of 1.1:1 and 1.6:1, respectively.

Table 2: Scope of the coupling of XantPhos Pd-G3 with various 1-thiosugars **1a-j**[a]



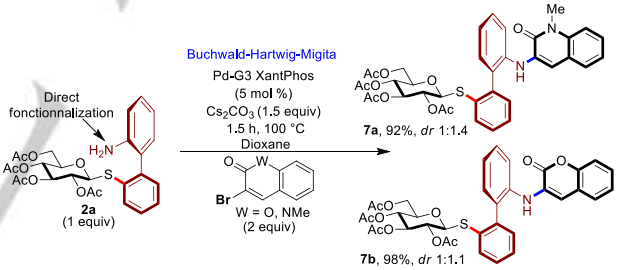
[a] Reactions of **1a-j** (2 equiv), XantPhos Pd-G3 (0.021 mmol, 1 equiv), in H_2O: THF (8:2, v/v) ([0.1M]) at 25 °C. [b] Yield of isolated product. [c] Ratio was determined by 1H NMR analysis. [d] Compound **2f** is not enough stable for full characterization (please see SI).

Having demonstrated the large scope of this procedure in regard of thiosugars, we examined in a further set of experiments, whether this reaction could be extended to other aryl and alkylthiol derivatives (Scheme 3). Thus, the coupling proceeds well with thiophenol **5a** within 20 min at room temperature, giving the coupled product **6a** in a 99% yield. In addition, we were pleased to find that non-aromatic thiols such as 2-(trimethylsilyl)ethane-1-thiol **5b** and *N*-Boc cysteine derivative **5c** could be reacted efficiently with the precatalyst XantPhos Pd-G3 furnishing **6b,c** in excellent yields. This last finding can be compared favorably to the recently reported procedure from Buchwald group who has disclosed that palladium(II) complexes could be used as a reagent (2-10 equiv) for selective cysteine conjugation.[15]



Scheme 3. Scope of the coupling of other thiols.

Finally, to illustrate the key advantage of this methodology, post-modifications of **2a** were undertaken through its residual aniline, which was exploited as a platform for molecular diversity (Scheme 4). Cross-coupling of the aniline of **2a** with haloheterocycles such as 3-bromocoumarin or 3-bromoquinolin-2H-one by using again Pd-G3 XantPhos as a catalyst in the presence of Cs_2CO_3 in dioxane at 100 °C, provided the desired 2,2'-biaryls in high yields and atropodistereomeric ratio 1.4:1 and 1.1.1, respectively (Scheme 2, substrates **7a,b**). The 3-aminoquinolin-2H-one **7a** may be regarded as analogues of 6BrCaQ, a potent hsp90 inhibitor developed in our laboratory.[16]



Scheme 4. Scope of the coupling of other thiols

In conclusion, we have developed an unprecedented method toward the synthesis 1-aminobiphenyl thioglycosides through a controllable activation of a Pd-G3-catalyst with various glycosylthiols. The reaction takes place rapidly (20 min) at room temperature with high selectivity. We expect this simple and general protocol to be of broad utility for the synthesis and development of new medicinal agents.

Experimental Section

Typical procedure for the coupling of thiosugars with Xantphos Pd-G3 pre-catalyst to synthesize compound (2a-j and 6a-c).

A flame dried sealable tube (5 ml) was charged with Xantphos Pd-G3 (20 mg, 0.021 mmol, 1.0 equiv) and 1-thiosugars or others thiols (15 mg, 0.042 mmol, 2 equiv). A solution of H_2O: THF (8:2; 168 µL, 0.25 mM) was added and the tube was sealed with a teflon screwcap, and the mixture was stirred at room temperature for 20

min. After evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography to afford the desired product.

Acknowledgements

Authors acknowledge support of this project by CNRS, University Paris Sud, ANR (ANR-15-CE29-0002) and by la Ligue Contre le Cancer through an Equipe Labellisée 2014 grant. We also thank the Iraqi Embassy for a doctoral fellow-ship to R.A.A.S. Our laboratory is a member of the Laborato-ry of Excellence LERMIT supported by a grant (ANR-10-LABX-33).

Keywords: Biaryl synthesis • thioglycosides • atropoisomers • thiosugars.

[1] a) Bringmann, G., Price Mortimer, A. J., Keller, P. A., Gresser, M. J., Garner, J., Breuning, M. *Angew. Chem. Int. Ed.*, **2005**, *44*, 5384-5427; b) Bringmann, G., Menche, D. *Acc. Chem. Res.*, **2001**, *34*, 615-624; c) Nicolaou, K. C., Bulger P. G., Sarlah, D. *Angew. Chem. Int. Ed.*, **2005**, *44*, 4442-4489; d) Roncali, J. *Chem. Rev.*, 1992, *92*, 711-738; e) Torssell, K. G. B. *Natural Product Chemistry,* 1983, Wiley, Chichester; (f) Ennis, D. S., McManus, J., Wood-Kaczmar, W., Richardson, J. Smith G. E., Carstairs, A. *Org. Process Res. Dev.*, **1999**, *3*, 248-252; g) Corbet J.-P., Mignani, G. *Chem. Rev.*, **2006**, *106*, 2651-2710; h) Hassan, J., Sevignon, M., Gozzi, C., Schulz E., Lemaire, M. *Chem. Rev.*, **2002**, *102*, 1359-1470; i) I. Cepanec in *Synthesis of Biaryls*, Elsevier, Amsterdam, 2004; j) Alberico, D., Scott M. E., Lautens, M. *Chem. Rev.*, **2007**, *107*, 174-238.

[2] a) Bemis G., W., Murcko, M. A. *J. Med. Chem.*, **1996**, *39*, 2887-2893; (b) Hajduk, P. J., Bures, M., Praestgaard J., Fesik, S. W. *J. Med. Chem.*, **2000**, *43*, 3443-3447; (c) Lloyd-Williams, P., Giralt, E. *Chem. Soc. Rev.*, **2001**, *30*, 145-157; d) Horton, D. A. Bourne G. T. Smythe, M. L. *Chem. Rev.*, **2003**, *103*, 893-930; e) Yasuda, N. *J. Organomet. Chem.*, **2002**, *653*, 279-287; f) Carey, J. S., Laffan, D., Thomson C., Williams, M. T. *Org. Biomol. Chem.*, **2006**, *4*, 2337-2347

[3] For biaryl as ligands, see: a) Martin R., Buchwald, S. L. *Acc. Chem. Res.*, **2008**, *41*, 1461-1473; b) Surry D. S., Buchwald, S. L. *Angew. Chem. Int. Ed.*, **2008**, *47*, 6338-6361; for biaryl as catalys, see c) Pu, L. *Chem. Rev.*, **1998**, *98*, 2405-2494; d) McCarthy, M., Guiry, P. J. *Tetrahedron*, **2001**, *57*, 3809-4058

[4] a) Kraft, A. Grimsdale, A. C., Holmes, A. B. *Angew. Chem. Int Ed*, 1998, *37*, 402-428; b) Roncali, J. *Chem. Rev.*, **1992**, *92*, 711-738; c) Blouin, N., Leclerc, M. *Acc. Chem. Res.*, **2008**, *41*, 1110-1119.

[5] a) Liu, B., Lee, Y., Zou, J., Petrassi, H. M., Joseph, R. W., Chao, W., Michelotti, E. L., Bukhtiyarova, M., Springman E. B., Dorsey, B. D. *Bioorg. Med. Chem. Lett.*, **2010**, *20*, 6592; b) Chen, S.-C., Kao, C.-M., Huang, M.-H., Shih, M.-K., Chen, Y.-L., Huang S.-P., Liu., T.-Z. *Toxicol. Sci.*, **2003**, *72*, 283-288; c) Wang, J.-B., Wu, Q.-Q., Min, Y.-Z., Liu Y.-Z., Song, Q.-H. *Chem. Commun.*, **2012**, *48*, 744746; d) Badawy, W. A., Ismail, K. M., Khalifa Z. M., Medany, S. S. *J. Appl. Polym. Sci.*, **2012**, *125*, 3410-3418; e) Hinterholzinger, F. M., Wuttke, S. Roy, P., Preusse, T., Schaate, A., Behrens, P. Godt A., Bein, T. *Dalton Trans.*, **2012**, *41*, 3899-3901; f) Schaate, A., Roy, P., Godt, A., Lippke, J., Waltz, F., Wiebcke M., Behrens, P. *Chem. Eur. J.*, **2011**, *17*, 6643-6651; g) Gao, H., Ess, D. H., Yousufuddin M., Kürti, L. *J. Am. Chem. Soc.*, **2013**, *135*, 7086-7089; h) Bryan, A. M., Merrill, W. A., Reiff, W. M., Fettinger J. C., Power, P. P. *Inorg. Chem.*, **2012**, *51*, 3366-3373.

[6] a) Catalytic Asymmetric Synthesis, 2nd ed.; Ojima, I., Ed.; Wiley: New York, NY, 2000; b) Noyori, R. *Angew. Chem. Int. Ed.*, **2002**, *41*, 2008-2022; c) Brunel, J. M. *Chem. Rev*. **2005**, *105*, 857-898.

[7] a) H.-R. Bjørsvik and V. Elumalai, *Eur. J. Org. Chem.*, **2016**, 5474; b) Suzuki, C. Hirano, K. Satoh T., Miura, M. *Org. Lett.*, **2015**, *17*, 1597-1600.

[8] Liang, Z., Zhang, J., Liu, Z., Wang K., Zhang, Y. *Tetrahedron*, **2013**, *69*, 6519-6526.

[9] Bu, M., Lu G., Cai, C. *Org. Chem. Front.*, **2016**, *3*, 630-544.

[10] Kumar, A., Sattar, M., Verma, A., Dara A., Kumar, S. *RSC Adv.*, **2015**, *5*, 44728-44741.

[11] Al-Shuaeeb, R. A. A., Kolodych, S., Koniev, O., Delacroix, S., Erb, S., Nicolaÿ, S., Cintrat, J.-C., Brion, J.-D., Cianférani, S., Alami, M., Wagner, A., Messaoudi, S. *Chem. Eur. J.*, **2016**, *22*, 11365-11370.

[12] a) Bruneau, A.; Brion, J.-D.; Alami, M.; Messaoudi, S. *Chem. Commun*. **2013**, *49*, 8359-8361. (b) Brachet, E.; Brion, J.-D.; Messaoudi, S.; Alami, M. *Adv. Synth. Catal*. **2013**, *355*, 477-490. c) Brachet, E.; Brion, J.-D.; Alami, M.; Messaoudi, S. *Chem. Eur. J*. **2013**, *19*, 15276-15280. d) Bruneau, A.; Roche, M.; Hamze, A.; Brion, J.-D.; Alami, M.; Messaoudi, S. *Chem. Eur. J.* **2015**, *21*, 8375-8379. e) Chabrier, A., Bruneau, A., Benmahdjoub, S., Benmerad, B., Belaid, S., Brion, J. D., Alami, M., Messaoudi, S., *Chem. Eur. J*., **2016**, *22*, 15006-15010. f) Luong, T. H.; Brion, J.-D.; Lescop, E.; Alami, M.; Messaoudi, S. *Org. Lett.* **2016**, *18*, 2126-2129.

[13] Bruneau, A., Roche, M., Alami, M., Messaoudi, S. *ACS Catalysis* **2015**, *5*, 1386-1396.

[14] The free energy of activation was calculated using the Gutowsky-Holm Equation: $\Delta G = aTc[9.972 + \log(Tc/Dn)$ where a = 4.575 x 10-3 kcal/mol or 1.914 x 10-2 kJ/mol, T*c* = coalescence temperature.

[15] Vinogradova, V., Zhang, C., Spokoyny, A. M., Pentelute B. L., S. L. Buchwald, *Nature*, **2015**, *526*, 687-691.

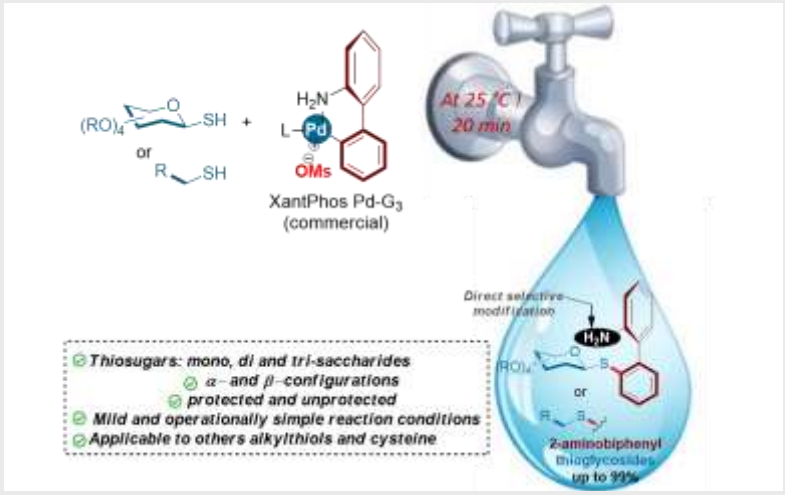
[16] Audisio, D., Messaoudi, S., Cegielkowski, L., Peyrat, J.-F., Brion, J.-D., Methy-Gonnot, D., Radanyi, C., Renoir, J.-M., Alami. M. *ChemMedChem*, **2011**, *6*, 804-815

10.1002/asia.201701415

WILEY-VCH

Layout 2:

COMMUNICATION



*Riyadh Ahmed Atto AL-Shuaeeb[]
Camille Dejean, Mouâd Alami,* and Samir Messaoudi**

Page No. – Page No.
Controllable activation of Pd-G3 palladacycle precatalyst in the presence of thiosugars: rapid access to 1-aminobiphenyl thioglycoside atropoisomers at room temperature