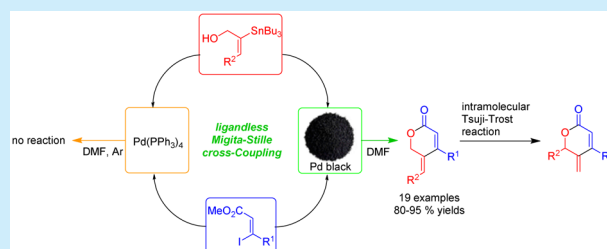


Fully Substituted Pyranones via Quasi-Heterogeneous Genuinely Ligand-Free Migita–Stille Coupling of Iodoacrylates

Jiří Kratochvíl,[†] Zdeněk Novák,[†] Mukund Ghavre,[†] Lucie Nováková,[‡] Aleš Růžička,[§] Jiří Kuneš,[†] and Milan Pour^{*,†}[†]Department of Inorganic and Organic Chemistry and [‡]Department of Analytical Chemistry, Faculty of Pharmacy, Charles University in Prague, Akademika Heyrovského 1203, Hradec Králové 500 05, Czech Republic[§]Department of General and Inorganic Chemistry, Faculty of Chemical Technology, University of Pardubice, Studentská 95, Pardubice 532 10, Czech Republic

S Supporting Information

ABSTRACT: Migita–Stille coupling of (*Z*)- β -iodoacrylates with (*E*)- α -stannyl allylic alcohols to furnish 5-alkylidene-4-substituted-5,6-dihydro-2*H*-pyran-2-ones is efficiently catalyzed by 2% Pd black in DMF, while Pd(PPh₃)₄ is inactive. Heterogeneous Pd released in solution is most likely responsible for the catalysis. The reaction is applicable to other substrates, without having to resort to ligands, additives, and/or solid support for Pd. The resulting pyranones can be rearranged to fully functionalized pyranones in another single step.



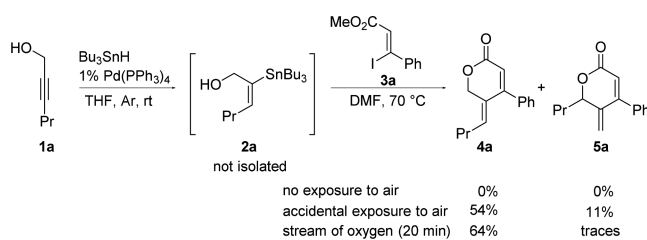
Migita–Stille coupling continues to be a popular Pd-catalyzed cross-coupling reaction. The majority of examples involve catalysis by a ligand-stabilized Pd⁰ species in solution.¹ On the other hand, the more attractive heterogeneous protocols² employing ligand-free Pd metal as the catalyst are limited to a few examples that utilize Pd on a solid support. Additionally, they suffer from several limitations. By way of example, catalysis using Pd/C requires the presence of AsPh₃/cuprous iodide³ or other additives (fluorides, LiCl) to achieve good yields,⁴ while Pd-doped KF/Al₂O₃ was subjected to MW irradiation in solvent-free conditions to a single substrate⁵ and Pd/CaCO₃ was reportedly used in the presence of tributylphenyltin only.⁶ An area of growing importance is Pd nanoparticles,⁷ which were prepared by the reduction of Pd^{II} salts and either encapsulated in a polymer matrix^{8a,b} or applied in an ionic liquid^{8c} when used in the Migita–Stille coupling.

Herein, we report a general cross-coupling catalyzed by colloidal Pd particles released from Pd black (2%) in DMF using (*Z*)- β -iodoacrylates. Interestingly, the reaction was inhibited by the presence of a phosphine under homogeneous conditions. The process allows an assembly of densely substituted pyranones in one step, and is also applicable to other substrate types. To the best of our knowledge, no reports of simple, unsupported commercially available Pd in its metallic form being employed as a catalyst in the Migita–Stille coupling have been published to date. Furthermore, the resulting pyranones can subsequently be converted to fully substituted heterocycles via PdL₄-mediated transfer of the substituent from the alkylidene group to C6.

Following our previous studies⁹ around the preparation of natural product like¹⁰ 5-alkylidenepyranone scaffolds, we reasoned that a properly tuned protocol employing Pd(PPh₃)₄-catalyzed hydrostannation of appropriate propargylic alcohols

followed by Migita–Stille coupling of resultant (*E*)-2-stannyl-2-en-1-ols with (*Z*)- β -iodoacrylates should deliver 5-alkylidene-4-substituted-5,6-dihydro-2*H*-pyran-2-ones in one pot (Scheme 1). Interestingly, coupling of β -iodoacrylates was reported only in a few cases, possibly due to their basic- and temperature-sensitive nature.¹¹

Scheme 1. Designed One-Pot Pyranone Synthesis



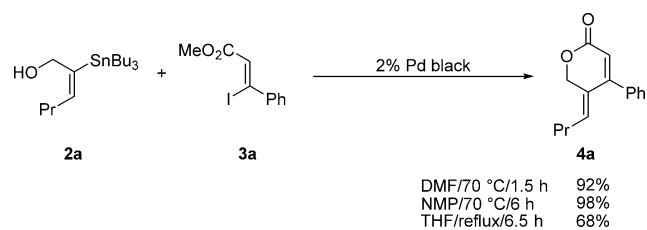
After some experimentation using propargylic alcohol 1a and ester 3a, where THF was replaced by DMF for the coupling step in order to promote the reaction, it came as a surprise that the coupling proceeded only when the mixture was accidentally exposed to air prior to addition of the iodoacrylate. The mixture turned black on account of formation of phosphine oxide and ensuing Pd black formation (Ph₃PO formation observed by ³¹P NMR). Upon workup, a mixture of the expected pyranone 4a and its isomer 5a was obtained. Furthermore, exposure to a stream of oxygen after hydrostannation resulted in complete phosphine oxidation and suppressed the formation of 5a. Since a

Received: December 8, 2014

control experiment confirmed that pure stannane **2a** did not react with iodoacrylate **3a** in the presence of freshly prepared $\text{Pd}(\text{PPh}_3)_4$ (1.6%) under Ar, with other conditions being identical, metallic Pd itself or a derived species must have acted as the catalyst. As the stability of oxidative adduct formed from iodoacrylates and $\text{Pd}(\text{PPh}_3)_4$ is well documented,¹² a conclusion can be drawn that its reactivity is insufficient for transmetalation with the organotin component.

Our next experiments were aimed at determining the activity of commercial Pd black in the coupling step and its recyclability. Coupling reactions performed in an NMR tube with varying amounts of Pd black (10, 5, 1, and 0.5%) in DMF-d_7 enabled us to determine the optimal amount of the catalyst and temperature (2% and 70 °C, respectively; see the Supporting Information). Then, stannane **2a** and acrylate **3a** were coupled in different solvents on a millimolar scale. DMF was the solvent of choice, and importantly, the absence of phosphine again resulted in no formation of **5a** (Scheme 2). Reuse of the recovered catalyst in the same reaction (5 times) led to comparable yields and marginally higher reaction time (see the Supporting Information).

Scheme 2. Solvent Optimization



Application of the optimized conditions to variously substituted derivatives of **2** and **3** (Table 1) showed that the reaction was tolerant of a wide range of functionalities (aryl, heteroaryl, alkyl, substituted alkyl) in both R^1 and R^2 , with high isolated yields (80–95%) achieved in most cases. Basic groups (**4n** and **4o**) were protected in order to prevent dehydroiodination of the acrylate (*t*-Boc group was used). Such compounds could be easily deprotected once the ring was constructed (**4n**).

In order to ascertain possible limitation of this methodology to relatively reactive (*Z*)- β -iodoacrylates, we performed series of experiments employing various types of stannanes and halides. The results showed that these conditions are generally applicable (Table 2). Again, a variety of functionalities were tolerated and the coupling proceeded even with aryl iodides bearing electron-donating substituents (**11** and **12**) and aryl bromides bearing electron-withdrawing substituents (**14** and **16**), although higher reaction temperatures were required in these cases.

In an attempt to improve the yield for substrates bearing electron-donating substituents, we briefly investigated the effect of additives (LiCl, LiF, TBAF; see the Supporting Information). Lithium chloride had a positive impact both on the yield and reaction time (Table 3).^{4,13} Moreover, the coupling of aryl chloride bearing an electron-withdrawing substituent was successfully performed. While we cannot strictly exclude Cl^- coordination to Pd in our system, it appears more likely that, given the amount of LiCl needed for significant rate enhancement and the heterogeneous conditions, Cl^- ions may act simply by increasing the polarity of the reaction mixture. A similar effect has been observed by Roy and Hartwig for Br^- ions in Kumada couplings and aminations.¹⁴

Table 1. Methodology Application: Lactones

R^1	R^2	time (h)	yield (%)	prod.
Pr	Ph	1,5	92	4a
Pr	H	0,4	87	4b
C_5H_{11}	4- $\text{O}_2\text{NC}_6\text{H}_4$	2,33	85	4c
CH_2OH	Pr	3	66	4d
CH_2OH	Ph	1,83	83	4e^a
CH_2OH	4- $\text{O}_2\text{NC}_6\text{H}_4$	3,5	72	4f
CH_2OH	4-MeOCOC $_6\text{H}_4$	3,33	79	4g
CH_2OH	3,4-diClC $_6\text{H}_3$	1,67	80	4h
	Ph	2	88	4i
	CH_2OH	2	66	4j
	H	2	95	4k
Bn	4-MeOCOC $_6\text{H}_4$	4,5	85	4l
$\text{Cl}(\text{CH}_2)_3$	Me	2,67	83	4m^b
	Ph	6	46	4n^c
$\text{BocNH}(\text{CH}_2)_3$	3,4-diClC $_6\text{H}_3$	2,67	86	4o
	Ph	3	72	4p

^aPerformed in gram scale. ^bEthyl ester used as starting material.

^cOverall yield (coupling and deprotection).

Nature of the catalysis was addressed as follows: First, Pd black was suspended in DMF, and the suspension was stirred for 3 h at 70 °C and subsequently filtered through a 100 nm filter to give a clear solution. The same filtration process was performed with the reaction mixture after the acrylate was consumed in coupling reaction, and both solutions were analyzed for the presence of Pd metal. Pd contents were determined by ICP-MS as 15 and 99 ppm of Pd, respectively. Hence, the presence of substrate gave rise to a significantly higher proportion of active Pd particles (<100 nm in diameter) in the mixture, the formation of which was very likely accelerated by oxidative addition.

Second, upon monitoring the reaction progress by NMR (see the Supporting Information), all curves showed an induction period independent of the amount of Pd black used, which indicates that the bulk metal is merely a precatalyst.¹⁵

Third, HPLC monitoring experiments were conducted (see the Supporting Information). Here the mixture was divided into 4 aliquots at approximately 50% conversion. The first aliquot was filtered through a 100 nm filter, a droplet of Hg was added to the second, the third was filtered and Hg then added, and the fourth was used as control. The HPLC analyses showed rapid termination of the cross-coupling process in both aliquots

Table 2. Methodology Application: General

$R^1-SnBu_3 + R^2-I \xrightarrow[DMF, 70^\circ C]{2\% \text{ Pd black}} R^1-R^2$		6-17		
R ¹	R ²	time (h)	yield (%)	prod.
		0,4	92	6
	4-MeOCOC ₆ H ₄	16	88	7
	4-O ₂ NC ₆ H ₄	3	85	8
	3,5-diNO ₂ C ₆ H ₃	3,5	92	9
	2-MeOCOC ₆ H ₄	42	59	10
	4-AcNHC ₆ H ₄	48	68	11 ^a
	4-MeOC ₆ H ₄	3,5	49	12 ^b
	2-MeOCOC ₆ H ₄	29	53	13 ^c
		4,5	50	14 ^{a,d}
Ph		4	96	15 ^e
Ph	4-COHC ₆ H ₄	7,33	80	16 ^{d,e,f}
2-furyl		0,2	96	17

^a90 °C. ^b110 °C. ^cAfter 21 h, temperature was raised to 90 °C. ^dAryl bromide was used as starting material. ^eTrimethylphenyltin was used as starting material. ^f100 °C.

containing Hg; the amount of Pd after the filtration dropped to 2.5 ppm. This is supportive for the heterogeneous catalysis. Furthermore, the kinetic curve of filtered experiment compared to control is essentially the same. Hence, particles larger than 100 nm in size can be excluded from the catalysis once the induction period is over, the presence of which again supports the hypothesis that there is an interaction between the Pd particle surface and the substrates.¹⁵

On the basis of these observations, a tentative conclusion can be drawn that Pd black releases colloidal particles smaller than 100 nm, which are probably responsible for the catalysis, and the formation of which is accelerated by the oxidative addition of the substrate.

Finally, the formation of pyranone of structural type 5 was investigated in a greater detail. We hypothesized that the compound was formed from lactone pattern 4 via an intra-

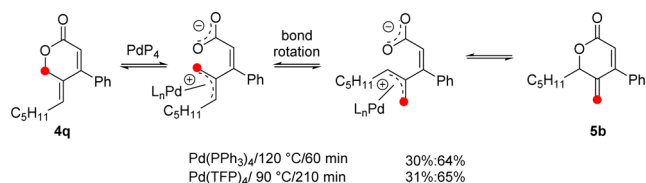
Table 3. Influence of LiCl

$R^1-SnBu_3 + R^2-X \xrightarrow[DMF]{2\% \text{ Pd black, LiCl (3 equiv.)}} R^1-R^2$				
R ¹	R ²	time (h)	yield (%)	prod.
		1,83	75	4 ^{a,b}
		24	82	11 ^{b,c}
	4-MeOC ₆ H ₄	2	79	12 ^{b,d}
Ph	4-COHC ₆ H ₄	5	91	16 ^{e,f}
Ph	4-COHC ₆ H ₄	6,5	60 (74) ^g	16 ^{h,i}

^a70 °C. ^bIodide was used as starting material. ^c90 °C. ^d110 °C. ^e100 °C. ^fBromide was used as starting material. ^g4% of Pd black was used. ^h140 °C. ⁱChloride was used as starting material.

molecular Tsuji–Trost reaction,¹⁶ when some PdL₄ catalyst remained in the mixture after incomplete phosphine oxidation. Indeed, when pyranone 4q was exposed to Pd(PPh₃)₄, partial conversion to 5b took place. The reaction proceeded under even milder conditions when Pd(TFP)₄ (TFP = tris-2-furylphosphine) was employed. While the experiment with ¹³C-labeled 4q (Scheme 3) supports the mechanism involving the formation of a

Scheme 3. Mechanistic Proposal for the Observed Tsuji–Trost Reaction



η^3 -allylic Pd complex that can be reattacked by the liberated carboxylate, the geometry of such compounds ignores stereo-electronic requirements for this process since alignment of the π orbitals of the double bond with the σ orbital of the leaving group is a prerequisite for the allylic substitution to occur.¹⁷ Following the X-ray study of the analogous derivative 4e, the σ orbital of the C–O bond is far from any alignment in both structural conformations present (calculated angles are 42,28° and 80,19°; see the Supporting Information).

Importantly, compound 5b possesses a fully functionalized pyranone core, capable of further elaboration into other structural types.

To conclude, we have found that Migita–Stille coupling of (Z)- β -iodoacrylates with (E)- α -stannyl allylic alcohols furnishes substituted pyranones in one step and is catalyzed by commercial Pd black most likely via the release of colloidal particles in solution, whereas Pd(PPh₃)₄ under homogeneous conditions is inactive. Since the process is also applicable to other types of substrates, commercially available, recyclable Pd black may be sufficient for a number of Migita–Stille cross-coupling cases, without the need for ligands and/or other additives. Finally, the

pyranones obtained can be further converted to synthetically versatile, fully substituted pyranones by a PdL₄ type of catalyst.

■ ASSOCIATED CONTENT

● Supporting Information

Experimental procedures, characterization data, and copies of NMR for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*Email: pour@faf.cuni.cz.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Charles University in Prague (Project Nos. GAUK 1176213 and SVV 260062), Czech Science Foundation (Project No. 15-07332S), and European Social Fund and the state budget of the Czech Republic (Project No. CZ.1.07/2.3.00/30.0061).

■ REFERENCES

- (1) (a) Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 6, 301–302. (b) Stille, J. K. *Angew. Chem.* **1986**, 98, 504–519. For a review on mechanisms, see: (c) Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, 43, 4704–4734. For a recent application, see: (d) Fu, C.; Zhang, Y.; Xuan, J.; Zhu, C.; Wang, B.; Ding, H. *Org. Lett.* **2014**, 16, 3376–3379. (e) Tanabe, Y.; Sato, E.; Nakajima, N.; Ohkubo, A.; Ohno, O.; Suenaga, K. *Org. Lett.* **2014**, 16, 2858–2861.
- (2) For a review on heterogeneous Pd catalysts in coupling reactions, see: Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, 107, 133–173.
- (3) (a) Roth, G. P.; Farina, V.; Liebeskind, L. S.; Peña-Cabrera, E. *Tetrahedron Lett.* **1995**, 36, 2191–2194. (b) Liebeskind, L. S.; Peña-Cabrera, E. *Org. Synth.* **2000**, 77, 135–140.
- (4) Yabe, Y.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Tetrahedron* **2010**, 66, 8654–8660.
- (5) Villemin, D.; Caillot, F. *Tetrahedron Lett.* **2001**, 42, 639–642.
- (6) Coelho, A. V.; de Souza, A. L. F.; de Lima, P. G.; Wardell, J. L.; Antunes, O. A. C. *Tetrahedron Lett.* **2007**, 48, 7671–7674.
- (7) For a recent review on nanoparticle catalysts in coupling reactions, see: Sydnies, M. O. *Curr. Org. Chem.* **2014**, 18, 312–326.
- (8) (a) Wu, L.; Li, Z.-W.; He, Y.-M.; Fan, Q.-H. *Adv. Synth. Catal.* **2008**, 350, 846–862. (b) Bernechea, M.; de Jesús, E.; López-Mardomingo, C.; Terreros, P. *Inorg. Chem.* **2009**, 48, 4491–4496. (c) Calo, V.; Nacci, A.; Monopoli, A.; Montingelli, F. *J. Org. Chem.* **2005**, 70, 6040–6044.
- (9) Pavlík, J.; Šnajdr, I.; Kuneš, J.; Špulák, M.; Pour, M. *J. Org. Chem.* **2009**, 74, 703–709.
- (10) (a) Lee, H.-J.; Chung, M.-C.; Lee, C.-H.; Yun, B.-S.; Chun, H.-K.; Kho, Y.-H. *J. Antibiot.* **1997**, 50, 357–359. (b) Brady, S. F.; Clardy, J. *J. Nat. Prod.* **2000**, 63, 1447–1448.
- (11) For examples of β -iodoacrylate eliminations in cross-coupling reactions, see: (a) Maw, G.; Thirsk, C.; Whiting, A. *Tetrahedron Lett.* **2001**, 42, 8387–8390. (b) Fáková, H.; Pour, M.; Kuneš, J.; Šenel, P. *Tetrahedron Lett.* **2005**, 46, 8137–8140. (c) Batsanov, A. S.; Knowles, J. P.; Whiting, A. *J. Org. Chem.* **2007**, 72, 2525–2532.
- (12) Rybin, L. V.; Petrovskaya, E. A.; Rubinskaya, M. I.; Kuz'mina, L. G.; Struchkov, Y. T.; Kaverin, V. V.; Koneva, N. Y. *J. Organomet. Chem.* **1985**, 288, 119–129.
- (13) The effect of Cl[−] ions in cross-coupling reactions under homogeneous conditions has been previously described: (a) Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, 33 (5), 314–321. (b) Amatore, C.; Azzabi, M.; Jutand, A. *J. Am. Chem. Soc.* **1991**, 113, 8375–8384.
- (14) (a) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, 125, 8704–8705. (b) Roy, A. H.; Hartwig, J. F. *Organometallics* **2004**, 23, 194–202.
- (15) For related observations, see: Widegren, J. A.; Finke, R. J. *J. Mol. Catal. A: Chem.* **2003**, 198, 317–341.
- (16) For reviews on this topic, see: (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, 103, 2921–2944. (b) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, 47, 258–297.
- (17) Farthing, C. N.; Kočovský, P. *J. Am. Chem. Soc.* **1998**, 120, 6661–6672.