



## Convenient Stille carbonylative cross-couplings using molybdenum hexacarbonyl

Jonas Lindh<sup>a</sup>, Ashkan Fardost<sup>a</sup>, Maria Almeida<sup>b</sup>, Peter Nilsson<sup>a,\*</sup>

<sup>a</sup>Organic Pharmaceutical Chemistry, Department of Medicinal Chemistry, Uppsala Biomedical Center, Uppsala University, PO Box 574, SE-751 23 Uppsala, Sweden

<sup>b</sup>Dirigentvägen 160, SE-756 54, Uppsala, Sweden

### ARTICLE INFO

#### Article history:

Received 21 December 2009

Revised 16 February 2010

Accepted 26 February 2010

Available online 3 March 2010

#### Keywords:

Stille

Molybdenum hexacarbonyl

Diaryl ketones

Palladium

### ABSTRACT

Palladium catalysis was used in Stille-type carbonylative cross-couplings employing Mo(CO)<sub>6</sub> as the carbon monoxide source. Robust and convenient transformations were carried out in closed vessels at 100 °C, providing a set of diaryl ketones in good yields. Aryl triflates and bromides were used as coupling partners with aryl stannanes. Inclusion of the Mo(CO)<sub>6</sub> destabilizing agent DBU made this protocol operationally simple and suppressed side-product formation.

© 2010 Elsevier Ltd. All rights reserved.

In the drug discovery process it is a common practice to synthesize focused series of congeners, based on a pharmacophore template, to explore the structure activity relationship for the target of interest. In this endeavor, it is of great importance to have access to reliable and robust synthetic methodologies, as very little time is usually available for reaction optimizations.<sup>1</sup>

Aiming for drug-space diversity, multi-component reactions such as metal-catalyzed carbonylations are often very effective, as they allow rapid systematic structural variations.<sup>2–5</sup> Additionally, isotopic labeling of CO (<sup>11</sup>C, <sup>13</sup>C, <sup>14</sup>C, <sup>17</sup>O, <sup>18</sup>O)<sup>6–11</sup> is a very powerful technique for the production of radiopharmaceuticals with excellent utility, for example, in positron emission tomography (PET) applications.<sup>12</sup>

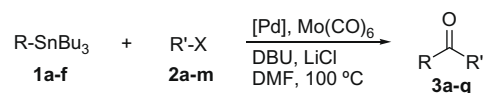
Regrettably, gaseous carbonylation reactions are often expensive and hazardous to perform in small-scale chemistry laboratories, in contrast to process chemistry laboratories where gaseous reactions are often simple to control and can be easily optimized. Hence, a solid carbon monoxide-releasing agent would make this two-phase reaction amenable to parallel synthesis on a milligram scale.<sup>8</sup> We have previously reported on a cobalt-catalyzed carbonylation<sup>13</sup> procedure to access diaryl ketones using solid Co<sub>2</sub>(CO)<sub>8</sub>.<sup>14</sup> Unfortunately this protocol, being rapid and high yielding, allowed only symmetrical aryl ketones<sup>15</sup> to be prepared. Herein, we report a method relying on the Stille carbonylative cross-coupling where a solid carbon monoxide source is used conveniently in closed vessels to obtain a variety of diaryl ketones (Scheme 1).

Aryl triflates are generally considered to be somewhat less reactive in carbonylative couplings than the corresponding iodides<sup>16</sup> and bromides.<sup>17,18</sup> Nevertheless, due to the facile preparation of aryl triflates from the parent phenols they constitute important potential aryl palladium precursors.<sup>19,20</sup>

After some experimentation, combining features from Stille's original protocol<sup>21</sup> and general metal carbonyl decomposing conditions, we found that 10 mol% of the palladium catalyst PdCl<sub>2</sub>(dppf)·CH<sub>2</sub>Cl<sub>2</sub> along with 1 equiv of Mo(CO)<sub>6</sub> and 10 mol% of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) gave full conversion and principally only carbonyl-inserted products. The use of LiCl as an additive was beneficial for reactions involving aryl triflates but was not required for those using aryl bromides.

The reactions were performed by simply mixing the chemicals, sealing the vessel, and heating the reaction according to Table 1, followed by a standard purification procedure.<sup>22</sup> Reaction times ranged between 16 and 24 h ensuring full conversion in all entries (except entry 6, vide infra) at 100 °C, and no individual optimization was performed.

Despite the use of only a small excess of carbon monoxide, byproducts originating from Stille biaryl coupling were rarely detected. This indicates that the solubility of carbon monoxide is

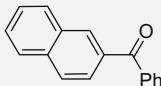

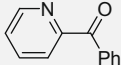
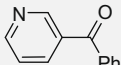
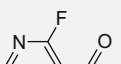
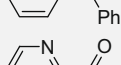
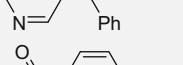
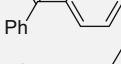
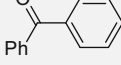
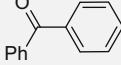
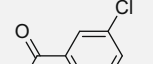
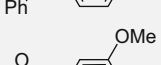
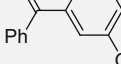
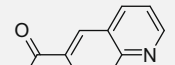
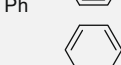
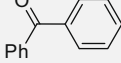
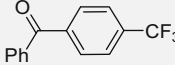
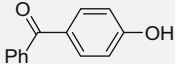


**Scheme 1.** Carbonylative coupling of electrophiles (X = OTf, Br) with organostannanes.

\* Corresponding author. Tel.: +46 184714338; fax: +46 18 4714474.

E-mail addresses: [peter.nilsson@orgfarm.uu.se](mailto:peter.nilsson@orgfarm.uu.se), [peter@orgfarm.uu.se](mailto:peter@orgfarm.uu.se) (P. Nilsson).

**Table 1**  
Carbonylative cross-coupling of organostannanes with various electrophiles<sup>a</sup> producing **3a–q** via Scheme 1

Entry	R–SnBu <sub>3</sub>	R	R'–X	Product RCOR'	Reaction time (h)	Isolated yield (%)
1	2-Naphthyl	<b>1a</b>	PhOTf	<b>2a</b>	16	 <b>3a</b> 79
2	Ph	<b>1b</b>	PhOTf	<b>2a</b>	16	 <b>3b</b> 72
3	2-Pyridyl	<b>1c</b>	PhOTf	<b>2a</b>	19	 <b>3c</b> 62
4	3-Pyridyl	<b>1d</b>	PhOTf	<b>2a</b>	16	 <b>3d</b> 72
5	2-Fluoro-3-pyridyl	<b>1e</b>	PhOTf	<b>2a</b>	16	 <b>3e</b> 42
6	Pyrazinyl	<b>1f</b>	PhOTf	<b>2a</b>	16	 <b>3f</b> 13
7	Ph	<b>1b</b>	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> OTf	<b>2b</b>	16	 <b>3g</b> 62
8	Ph	<b>1b</b>	<i>m</i> -Tol-OTf	<b>2c</b>	16	 <b>3h</b> 73
9	Ph	<b>1b</b>	<i>p</i> -Tol-OTf	<b>2d</b>	16	 <b>3i</b> 83
10	Ph	<b>1b</b>	<i>m</i> -ClC <sub>6</sub> H <sub>4</sub> OTf	<b>2e</b>	24	 <b>3j</b> 91
11	Ph	<b>1b</b>	3,5-di-(MeO)C <sub>6</sub> H <sub>3</sub> OTf	<b>2f</b>	16	 <b>3k</b> 90
12	Ph	<b>1b</b>	Quinoline-6-triflate	<b>2g</b>	16	 <b>3l</b> 98
13	Ph	<b>1b</b>	1-Naphthyl triflate	<b>2h</b>	16	 <b>3m</b> 78
14	Ph	<b>1b</b>	<i>p</i> -CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> OTf	<b>2i</b>	16	 <b>3n</b> 94
15	Ph	<b>1b</b>	<i>p</i> -Bromophenol	<b>2j</b>	16	 <b>3o</b> 67
16	Ph	<b>1b</b>	<i>m</i> -Bromoanisole	<b>2k</b>	16	 <b>3p</b> 36
17	Ph	<b>1b</b>	<i>p</i> -Bromobenzotrifluoride	<b>2l</b>	16	 <b>3n</b> 80
18	Ph	<b>1b</b>	<i>p</i> -Bromoacetophenone	<b>2m</b>	16	 <b>3q</b> 73

<sup>a</sup> The reaction was conducted in closed vessels at 100 °C on 1 mmol scale (**2a–m**) with 1.4 equiv of **1a–f**, 10 mol % PdCl<sub>2</sub>(dppf)<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub>, 1 equiv of Mo(CO)<sub>6</sub>, 10 mol % DBU, 1.4 equiv of LiCl in DMF (5 mL).

sufficient in DMF, at the temperature used, to retain enough of the gas in solution. The limited expenditure of carbon monoxide can be a very important feature, from a cost perspective, when isotopically labeled CO is utilized.<sup>8,9</sup> Low partial CO pressure is also beneficial for the catalytic effectiveness because excessive Pd–CO association reduces the equilibrium concentration of the catalytically active electron-rich Pd(0) species involved in the oxidative addition step.

The stability of the catalytic system is manifested through the efficiency by which possibly chelating pyridine substrates are coupled in high yields (entries 3–6 and 12), as pyridines are known to be good coordinating ligands to both molybdenum<sup>23,24</sup> and palladium.<sup>25</sup> Running the reaction without DBU, as the carbon monoxide release promoter, resulted in a somewhat lower yield of benzophenone (68% vs 72%, entry 2) and formation of a biaryl side-product was detected.<sup>26</sup> Performing the reaction with 0.5 equiv of Mo(CO)<sub>6</sub> gave incomplete conversion and a reduced yield of benzophenone (58% vs 72%). Also substantial biaryl formation was detected here.

It has been suggested in the literature that initial complexation of metal carbonyls to arenes, yielding in our case  $\eta^6$ -ArXMo(CO)<sub>3</sub>, followed by oxidative addition of palladium with subsequent internal migration of CO into the Pd–Ar bond is a conceivable reaction pathway.<sup>27,28</sup> However, as mentioned, a substoichiometric amount (0.5 equiv) of Mo(CO)<sub>6</sub> provided a 58% yield, thus the involvement of molybdenum in the catalytic cycle seems less likely under our conditions.<sup>29</sup>

Electron-rich and neutral stannanes produced satisfying yields and no de-stannylated starting material was found (entries 1 and 2). It is notable that, in contrast to the original report by Stille, electron-poor aryl stannanes perform well in the coupling with phenyl triflate (entries 3–5) employing our general protocol.<sup>21</sup> Furthermore, all the employed electron-poor aryl triflates performed well (entries 10–14).<sup>15</sup> Electron-rich and neutral aryl triflates gave slightly lower yields (entries 2 and 7–9). The only disappointment was the coupling with pyrazine stannane (entry 6), where full conversion was not achieved, providing only 13% of isolated product and substantial amounts of unreacted starting material.

To further define the scope of our catalytic carbonylation protocol we decided to include aryl bromides, which are readily available, more stable, and cheaper than the corresponding iodides. As expected, aryl bromides were found to be comparably productive coupling partners in our system. Good yields (36–80%) were obtained using both electron-rich and electron-poor substrates (entries 15–18). Importantly, running the reaction with phenol **2j** (entry 15), the only product obtained was the desired diaryl ketone. No trace of the ester product (4-bromophenyl benzoate) could be detected upon LC–MS analysis of the crude mixture. A more expected chemoselectivity was obtained in entry 10 where the chlorine proved inert to the coupling conditions. This pronounced substrate chemoselectivity can prove very important when assembling complex molecules and may circumvent the need for protecting group strategies.

In conclusion, we have successfully developed a synthetically convenient and flexible protocol for carbonylative Stille diaryl couplings employing a solid CO-source. Aryl triflates showed broad scope producing high yields and also allowed couplings with electron-poor aryl tin reagents. To the best of our knowledge, this is the

first report where electron-poor aryl tin reagents such as 2-pyridylstannane **1c** are successfully employed in carbonylative Stille cross-couplings. A wide variety of diaryl ketones were produced, in good to high yields, employing a single standard protocol for both aryl triflates and bromides. Further investigations are currently ongoing in our laboratory to explore the scope and limitations of this reaction.

## Acknowledgments

We thank Dr. Luke Odell for critically reviewing this Letter and the Knut and Alice Wallenberg Foundation for helpful support of this investigation.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.165.

## References and notes

- Moriello, A. S.; Balas, L.; Ligresti, A.; Cascio, M. G.; Durand, T.; Morera, E.; Ortar, G.; Di Marzo, V. *J. Med. Chem.* **2006**, *49*, 2320–2332.
- Barnard, C. F. *J. Organometallics* **2008**, *27*, 5402–5422.
- Brennfuehrer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114–4133.
- Doi, T.; Inoue, H.; Tokita, M.; Watanabe, J.; Takahashi, T. *J. Comb. Chem.* **2008**, *10*, 135–141.
- Yun, W.; Li, S.; Wang, B.; Chen, L. *Tetrahedron Lett.* **2001**, *42*, 175–177.
- Al-Qahtani, M. H.; Pike, V. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1033–1036.
- Al-Qahtani, M. H.; Pike, V. W. *J. Labelled Compd. Radiopharm.* **2000**, *43*, 825–835.
- Darensbourg, D. J.; Walker, N.; Darensbourg, M. Y. *J. Am. Chem. Soc.* **1980**, *102*, 1213–1214.
- Bricker, J. C.; Payne, M. W.; Shore, S. G. *Organometallics* **1987**, *6*, 2545–2547.
- Elmore, C. S.; Dean, D. C.; Melillo, D. G. *J. Labelled Compd. Radiopharm.* **2000**, *43*, 1135–1144.
- Dobson, R. L.; Kelm, G. R.; Neal, D. M. *Biol. Mass Spectrom.* **1994**, *23*, 75–81.
- Karimi, F.; Långström, B. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2111–2116.
- Enquist, P.-A.; Nilsson, P.; Edin, J.; Larhed, M. *Tetrahedron Lett.* **2005**, *46*, 3335–3339.
- Enquist, P.-A.; Nilsson, P.; Larhed, M. *Org. Lett.* **2003**, *5*, 4875–4878.
- Neumann, H.; Brennfuehrer, A.; Beller, M. *Chem. Eur. J.* **2008**, *14*, 3645–3652.
- Karimi, F.; Barletta, J.; Langstroem, B. *Eur. J. Org. Chem.* **2005**, 2374–2378.
- Wu, X.; Nilsson, P.; Larhed, M. *J. Org. Chem.* **2005**, *70*, 346–349.
- Wu, X.; Ekegren, J. K.; Larhed, M. *Organometallics* **2006**, *25*, 1434–1439.
- Ritter, K. *Synthesis* **1993**, 735–762.
- Odell, L. R.; Sävmarker, J.; Larhed, M. *Tetrahedron Lett.* **2008**, *49*, 6115–6118.
- Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 1557–1565.
- Typical experimental procedure:* To a 5 mL process vial were added aryl triflate (1.0 mmol), aryltributyltin (1.4 mmol), PdCl<sub>2</sub>(dppf)<sub>2</sub>·CH<sub>2</sub>Cl<sub>2</sub> (81.6 mg, 0.1 mmol), Mo(CO)<sub>6</sub> (264 mg, 1.0 mmol), DBU (15 mg, 0.1 mmol), LiCl (59 mg, 1.4 mmol), and DMF (5 mL). The vial was sealed with a septum and the reaction mixture was heated in a heating block with stirring at 100 °C for the time denoted in Table 1. The reaction was cooled to rt and the DMF was carefully evaporated. The crude reaction mixture was purified by silica gel chromatography.
- Adedeji, F. A.; Connor, J. A.; Demain, C. P.; Martinho-Simoës, J. A.; Skinner, H. A.; Moattar, M. T. *Z. J. Organomet. Chem.* **1978**, *149*, 333–343.
- Pearson, A. J.; Schoffers, E. *Organometallics* **1997**, *16*, 5365–5367.
- Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2001**, *123*, 8217–8225.
- Wannberg, J.; Larhed, M. *J. Org. Chem.* **2003**, *68*, 5750–5753.
- Caldirola, P.; Chowdhury, R.; Johansson, A. M.; Hacksell, U. *Organometallics* **1995**, *14*, 3897–3900.
- Holmberg, P.; Sohn, D.; Leideborg, R.; Caldirola, P.; Zlatoidsky, P.; Hanson, S.; Mohell, N.; Rosqvist, S.; Nordvall, G.; Johansson, A. M.; Johansson, R. *J. Med. Chem.* **2004**, *47*, 3927–3930.
- Takaya, J.; Sangu, K.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 7090–7093.