ChemComm

This article is part of the

New advances in catalytic C–C bond formation via late transition metals web themed issue

Guest editor: Professor Michael Krische

All articles in this issue will be gathered together online at <u>www.rsc.org/catalytic_CC</u>.



Cite this: Chem. Commun., 2011, 47, 12679-12681

COMMUNICATION

Synthesis of diaryl ketones via a phosphine-free Fukuyama reaction †‡

Kamala Kunchithapatham, Chad C. Eichman and James P. Stambuli*

Received 1st October 2011, Accepted 17th October 2011 DOI: 10.1039/c1cc16114h

The synthesis of unsymmetrical diaryl ketones *via* the Fukuyama coupling of thioesters and organozinc reagents is described. Typically, the synthesis of diaryl ketones using this methodology provides low yields. The simple complex, Pd(dba)₂, was found to convert a variety of aryl thioesters to diaryl ketones in good yields.

Palladium-catalyzed cross-coupling reactions offer synthetic chemists the ability to construct carbon–carbon and carbon–heteroatom bonds in a highly efficient and predictable manner. In general, most methods to construct C–C bonds through palladium-catalyzed processes involve the coupling of an organohalide with an organometallic or organometalloid species.¹ Fukuyama reported a method to form C–C bonds using thioesters as a coupling partner in place of aryl halides.^{2–5} This cross-coupling reaction proceeds through C–S bond activation of the thioester followed by transmetallation with an organozinc reagent, and reductive elimination to provide the desired product. This mild method furnishes high yields of many ketones at ambient temperatures (Scheme 1).

In addition to the Fukuyama reaction, Liebeskind and Srogl developed a protocol to prepare diaryl ketones from the corresponding thiol esters and boronic acids.^{6,7} This method requires excess copper reagent in addition to the palladium catalyst, and did not work for our purposes. Iron has also been utilized to cross-couple thioesters.⁸ However, acyl chlorides were used to form diaryl ketones. The use of nickel to form diaryl ketones from a thioester has also been described, but the reported conditions provided ester-containing substrates in low yields.⁹ Despite the various reports of Fukuyama crosscouplings and the broad scope of this reaction, a general method to prepare diaryl ketones using this methodology is absent from the literature. In Fukuyama's original reports, diaryl ketones were not listed. A single example employing phenylzinc bromide was coupled with an alkyl thioester to give only 50% of the desired ketone product using 10 mol% PdCl₂(PPh₃)₂ as catalyst.⁴

The diaryl ketone is an important moiety embedded in medicinal compounds,¹⁰ such as ketoprofen and suprofen. Recently, we desired a mild method to prepare the diaryl ketone (**2a**), which contains an ester functionality. Surveying current literature routes to access diaryl ketones,^{8–33} the mild conditions for the Fukuyama reaction would provide straightforward access to **2a**. Although diaryl ketones were not commonly published using Fukuyama conditions, expansion of this method to cover diaryl ketone substrates would be a useful extension. Through this reaction optimization, conditions for a phosphine-free Fukuyama reaction was discovered that produces good to high yields of functionalized, unsymmetrical diaryl ketones.

Compound **1a** was prepared from the corresponding acid in near quantitative yield. Treating **1a** under the standard conditions reported for the Fukuyama coupling reaction resulted in incomplete reaction conversion and formation of the desired diarylketone **2a** in only a 30% isolated yield (eqn (1)). The conversion to product was low, likely a result of the selfconsumption of the organozinc reagent, as a significant amount of biphenyl was formed during the reaction. Employing DMF as a solvent in the reaction only slightly increased reaction yield, as 35% of diaryl ketone **2a** was isolated.



We turned our attention to catalyst modification to improve reaction yield. After an extensive ligand screening, the palladium dimer containing 10 mol% tri-*tert*-butylphosphine ($[Pd(P'Bu_3)Br]_2$) was initially identified as the optimal ligand for reaction conversion (Table 1, entry 2). Employing ligands such as triphenylphosphine (PPh_3), 1,1'-bis(diphenylphosphino)ferrocene (dppf), tri-*ortho*-tolylphosphine (P(*o*-tol)_3), and tri-(2-furyl)phosphine (TFP) all gave inferior results



Scheme 1 Fukuyama reaction for the synthesis of ketones.

reaction optimization tables. See DOI: 10.1039/c1cc16114h

Department of Chemistry, The Ohio State University,

¹⁰⁰ West 18th Avenue, Columbus, Ohio 43210, United States. E-mail: stambuli@chemistry.ohio-state.edu

 [†] This article is part of the *ChemComm* 'Advances in catalytic C–C bond formation *via* late transition metals' web themed issue.
 ‡ Electronic supplementary information (ESI) available: Experimental procedures, characterization of newly synthesized compounds, and



^{*a*} Reaction performed on 1 mmol scale of thioester with 1.2 equiv. arylzinc reagent. ^{*b*} P:SM is the ratio of product to starting material as monitored by ¹H NMR spectroscopy.

(see Supporting Information). We were pleased to find that a significant reduction in catalyst loading (0.2 mol%) provided excellent reaction conversion (entry 3). As a control, the use of a palladium complex (Pd(dba)₂) lacking a phosphine ligand was screened to investigate the necessity of an external phosphine ligand. Surprisingly, employment of 1 mol% of $Pd(dba)_2$ in toluene at ambient temperature provided high conversion of starting material (1a) to product (2a) (entry 4). Decreasing the amount of the Pd(dba)₂ catalyst to 0.5 mol% significantly decreased reaction conversion (entry 5). To our knowledge, this is the first report of a Fukuyama reaction catalyzed simply by $Pd(dba)_2$. There has been a report of the use of Pd/C to promote this reaction,²⁹ but this catalyst did not work well under our reaction conditions. Moreover, the reported Pd/C catalyst has not been shown to be an efficient catalyst to prepare diaryl ketones.

The solubility of $Pd(dba)_2$ in most organic solvents is typically poor. Therefore, the use of $Pd(dba)_2$ as a catalyst

 Table 2
 Reaction scope for Pd(dba)₂-catalyzed Fukuyama reaction^a



for coupling reactions without external ligands is rare. The reaction scope to produce diaryl ketones was examined using catalytic Pd(dba)₂.

The reaction provided good yields of various diaryl ketone products with $Pd(dba)_2$ as catalyst (Table 2). The reaction proceeded smoothly in the presence of methyl esters and heterocyclic functional motifs to provide diaryl ketones **2a**, **2b**, **2c**, and **2g** in good yields. The electronics of the aryl thioester or the aryl zinc reagent did not have a dramatic effect on the course of the reaction, as almost all cases gave good yields of diaryl ketone products. Notably, sterically hindered diaryl ketones are readily produced in this reaction without requiring an increase in reaction temperature or catalyst loading (**2h–2j**).

We were interested in probing the selectivity of the thioester moieties in the presence of aryl halides under these new

Table 3 Fukuyama and Negishi reactions of thioesters in the presence of aryl halides^a



^a Yields are an average of two reactions at 1 mmol scale.

catalytic conditions. We suspected that a complex mixture of products may be produced if an aryl halide were appended to the aromatic ring containing the thioester. Under the phosphinefree conditions, a complex mixture of products was indeed observed. However, upon addition of tri-2-furylphosphine as ligand, a selective process was uncovered. Employing thioesters containing appended aryl bromides, the cross-coupling proceeded to yield diaryl ketones in good yields using 0.5 mol% Pd(dba)₂ and 0.7 mol% tri-2-furylphosphine (2k-m, Table 3). In contrast, with an aryl iodide present, complete conversion to a biaryl Negishi product was observed (3n-3g). Finally, compound 3p, produced from the coupling of the thioester of 3-bromo-5-iodobenzoic acid with o-anisyl zinc reagent, retains both the reactive thioester functionality and the aryl bromide that can be employed in additional cross-coupling reactions. These results suggest that thioesters are more reactive towards oxidative addition than aryl bromides.

In summary, we have described significant improvements in the diaryl ketone synthesis *via* the Fukuyama reaction. The use of $Pd(dba)_2$ without an external ligand provided an active catalyst that promoted the formation of diaryl ketones in good to high yields at ambient temperature. The chemoselectivity of this reaction was also investigated by employing thioester substrates containing aryl halides. In the presence of aryl iodides, the major product arose from a Negishi cross-coupling reaction, whereas in the presence of aryl bromides, the major product arose from a Fukuyama coupling at the thioester.

We gratefully acknowledge The Ohio State University for support of this research, and Johnson Matthey for generously providing $([Pd(P'Bu_3)Br]_2)$.

Notes and references

- 1 J. F. Hartwig, Organotransition Metal Chemistry: From Bonding to Catalysis, University Science Books, Sausalito, 2010.
- 2 T. Fukuyama, T. Miyazaki, Y. Han-ya and H. Tokuyama, *Synlett*, 2004, 477–480.
- 3 T. Fukuyama and H. Tokuyama, Aldrichim Acta, 2004, 37, 87-96.
- 4 T. Fukuyama, H. Tokuyama, S. Yokoshima and T. Yamashita, *Tetrahedron Lett.*, 1998, **39**, 3189–3192.
- 5 H. Tokuyama, S. Yokoshima, T. Yamashita, S. C. Lin, L. P. Li and T. Fukuyama, J. Braz. Chem. Soc., 1998, 9, 381–387.
- 6 L. S. Liebeskind and J. Srogl, J. Am. Chem. Soc., 2000, 122, 11260–11261.

- 7 J. Srogl, C. Savarin and L. S. Liebeskind, Org. Lett., 2000, 2, 3229–3231.
- 8 (a) C. Cardellicchio, V. Fiandese, G. Marchese and L. Ronzini, *Tetrahedron Lett.*, 1987, **28**, 2053–2056; (b) V. Fiandese, G. Marchese and F. Naso, *Tetrahedron Lett.*, 1988, **29**, 3587–3590.
- 9 T. Shimizu and M. Seki, *Tetrahedron Lett.*, 2002, **43**, 1039–1042.
- 10 H. Neumann, A. Brennfuhrer and M. Beller, *Adv. Synth. Catal.*, 2008, **350**, 2437–2442.
- 11 D. H. R. Barton, N. Ozbalik and M. Ramesh, *Tetrahedron*, 1988, 44, 5661–5668.
- 12 M. Beller, H. Neumann and A. Brennfuehrer, *Chem.-Eur. J.*, 2008, 14, 3645–3652.
- 13 N. A. Bumagin and D. N. Korolev, *Tetrahedron Lett.*, 1999, 40, 3057–3060.
- 14 C. H. Cheng, Y. C. Huang and K. K. Majumdar, J. Org. Chem., 2002, 67, 1682–1684.
- 15 C. H. Cheng, J. Karthikeyan and K. Parthasarathy, *Chem. Commun.*, 2011, **47**, 10461–10463.
- 16 R. K. Dieter, Tetrahedron, 1999, 55, 4177-4236.
- 17 A. M. Echavarren and J. K. Stille, J. Am. Chem. Soc., 1988, 110, 1557–1565.
- 18 V. Fiandanese, G. Marchese, V. Martina and L. Ronzini, *Tetrahedron Lett.*, 1984, 25, 4805–4808.
- 19 J. P. Genet, O. Chuzel, A. Roesch and S. Darses, *J. Org. Chem.*, 2008, **73**, 7800–7802.
- 20 L. J. Goossen and K. Ghosh, Angew. Chem., Int. Ed., 2001, 40, 3458-3462.
- 21 J. F. Hartwig and A. Takemiya, J. Am. Chem. Soc., 2006, 128, 14800–14801.
- 22 Y. Hatanaka, S. Fukushima and T. Hiyama, *Tetrahedron*, 1992, 48, 2113–2126.
- 23 S. P. Hollinshead, J. B. Nichols and J. W. Wilson, J. Org. Chem., 1994, 59, 6703–6709.
- 24 P. Knochel, C. Duplais, F. Bures, I. Sapountzis, T. J. Korn and G. Cahiez, *Angew. Chem.*, *Int. Ed.*, 2004, **43**, 2968–2970.
- 25 M. T. Lockhart, M. J. Lo Fiego, G. F. Silbestri and A. B. Chopa, J. Org. Chem., 2011, 76, 1707–1714.
- 26 S. F. Martin, B. M. O'Keefe and N. Simmons, Org. Lett., 2008, 10, 5301–5304.
- 27 N. Miyaura, T. Ishiyama, H. Kizaki, T. Hayashi and A. Suzuki, J. Org. Chem., 1998, 63, 4726–4731.
- 28 T. Rovis and Y. D. Zhang, J. Am. Chem. Soc., 2004, 126, 15964–15965.
- 29 M. Seki and Y. Mori, Adv. Synth. Catal., 2007, 349, 2027-2038.
- 30 G. F. Silbestri, R. B. Masson, M. T. Lockhart and A. B. Chopa, J. Organomet. Chem., 2006, 691, 1520–1524.
- 31 D. F. Taber and M. R. Sethuraman, J. Org. Chem., 2000, 65, 254–255.
- 32 M. Yang, H. L. Li, Y. X. Qi and J. J. Xue, E. J. Org. Chem., 2011, 2662–2667.
- 33 L. J. Zhang, Y. Z. Huang, H. X. Jiang, D. M. Jun and L. Yi, J. Org. Chem., 1992, 57, 774–777.