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# Pd-catalyzed α-arylation of thioamides

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ABSTRACT

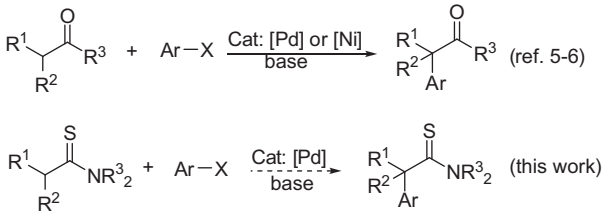
Thioamides are unique and versatile synthetic building blocks with S, N, and α-C three adjacent nucleophile centers, however, they are rarely used as carbon nucleophiles for transition-metal-catalyzed C–C coupling reactions. This Letter describes the first Pd-catalyzed α-arylation of thioamides and demonstrated the feasibility of the application of thioamides in coupling chemistry. By the coupling process, a variety of α-arylated thioamides were prepared in moderate to good yields under mild reaction conditions, which provides an alternative way to access functionalized thioamides as well as a new synthetic transformation for thioamides. High chemoselectivity for thioamide over amide was observed in the reaction.



Thioamides are important synthetic building blocks with sulfur, nitrogen, and α-carbon three adjacent nucleophilic centers, which have been extensively used to synthesize a wide variety of significant molecules, especially to construct various heterocyclic compounds, by reaction with many kinds of electrophiles.[1,2] Although thioamides have displayed wide applications in organic synthesis,[1,2] they are rarely used as carbon nucleophiles for transition-metal-catalyzed C–C coupling reactions.[3–5] Pd- and Ni-catalyzed α-arylation of carbonyl compounds has emerged as one of the most useful synthetic tools for $sp^2$–$sp^3$ C–C bond formation (Scheme 1).[5,6] However, the corresponding Pd- and Ni-catalyzed α-arylation of thioamides has not been explored so far (Scheme 1). As compared to structurally related amides, thioamides have more acidic α-protons[7] and higher coordination abilities to transition metal centers, which might lead to specific reactivities and unique selectivities for thioamides in transition-metal-catalyzed C–C coupling reactions. Moreover, thioamides can be facilely transformed into many other vital functional groups including amines,[4a,8] aldehydes,[4c,9] amides,[10] acids,[11] thioesters,[12] and β-ketoesters.[4c,13] Considering the synthetic importance, unique properties, and facile functionalization of thioamides, it should be highly desirable to explore Pd-catalyzed α-arylation of thioamides. Herein, we wish to report our preliminary studies on this project.

Initial investigation was carried out with *N*,*N*-dimethyl-3-phenylpropanethioamide (**1a**) and iodobenzene (**2a**) by using $Pd(PPh_3)_4$ as catalyst (Table 1, entry 2). The α-arylation of thioamide **1a** occurred in 86% conversion. Further screening showed that the palladium catalyst was necessary for the transformation (Table 1, entry 1 vs 2). $[Pd(C_3H_5)Cl]_2$ was the most efficient catalyst. The sulfur atom of thioamide did not poison the palladium catalyst at all. Phosphine ligand also played an important role in the reaction (Table 1, entry 8 vs entries 7 and 9–11) and $PPh_3$ was the choice of the ligand for the α-arylation of thioamides (Table 1, entry 7).

Substrate scope was then investigated by using $[Pd(C_3H_5)Cl]_2$-$PPh_3$ as catalyst (Table 2). Various thioamides were smoothly α-arylated to give the corresponding coupling products in moderate to good yields under the optimized conditions.[14] Aryl bromides were as active as iodobenzene in the α-arylation of thioamides. However, aryl chloride such as chlorobenzene (**2e**) was totally ineffective for the reaction (Table 2, entry 10). Functional groups such as C–C double bond and OTBS were well tolerated by the reaction (Table 2, entries 13 and 14). High selectivity in monoarylation was observed in the reaction and no diarylated product was isolated in all cases. Disubstituted thioamides such as *N*,*N*-dimethyl-2-ethylhexanethioamide are not effective for the α-arylation under the




**Scheme 1.**

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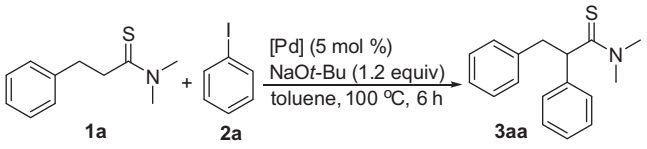
**Table 1**
Screening of reaction conditions for Pd-catalyzed α-arylation of thioamides[a]

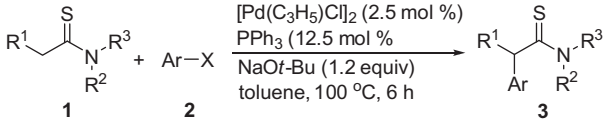



1a 2a 3aa

| Entry | [Pd] | Ligand | Conv.[b] (%) |
|---|---|---|---|
| 1 | None | $PPh_3$ | 0 |
| 2 | $Pd(PPh_3)_4$ | — | 86 |
| 3 | $Pd_2(dba)_3$ | $PPh_3$ | 68 |
| 4 | $Pd(OAc)_2$ | $PPh_3$ | 94 |
| 5 | $PdCl_2$ | $PPh_3$ | 80 |
| 6 | $Pd(C_6H_5CN)_2Cl_2$ | $PPh_3$ | 83 |
| 7 | $[Pd(C_3H_5)Cl]_2$ | $PPh_3$ | 96 |
| 8 | $[Pd(C_3H_5)Cl]_2$ | — | 0 |
| 9 | $[Pd(C_3H_5)Cl]_2$ | $PCy_3$ | 70 |
| 10 | $[Pd(C_3H_5)Cl]_2$ | $P(OPh)_3$ | 40 |
| 11 | $[Pd(C_3H_5)Cl]_2$ | dppb | 74 |

[a] All the reactions were carried out with *N*,*N*-dimethyl-3-phenylpropanethioamide (**1a**) (0.40 mmol), iodobenzene (**2a**) (1.0 mmol), NaO*t*-Bu (0.48 mmol), Pd (0.020 mmol), and ligand (0.050 mmol for monodentate ligand and 0.025 mmol for dppb) in toluene (2 mL) at 100 °C for 6 h unless otherwise stated.
[b] The conversion was based on thioamide **1a** and determined by $^1$H NMR analysis of the crude reaction mixture.

**Table 2**
Pd-catalyzed α-arylation of thioamides[a]




1 2 3

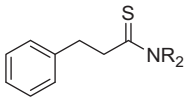
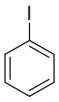
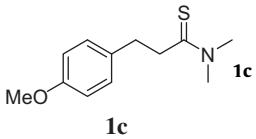
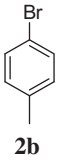
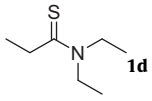
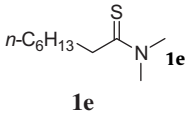
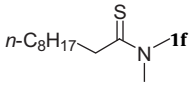
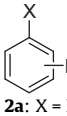
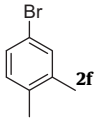
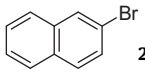
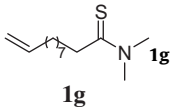
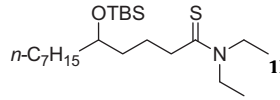
| Entry | Thioamide (**1**) | ArX (**2**) | Yield[b] (%) |
|---|---|---|---|
| 1 |  **1a**: R = Me |  **2a** | 60 |
| 2 | **1b**: R = Et | **2a** | 60 |
| 3 |  **1c** |  **2b** | 52 |
| 4 |  **1d** | **2a** | 63 |
| 5 |  **1e** | **2a** | 62 |
| 6 |  **1f** |  **2a**: X = I, R = H | 64 |
| 7 | **1f** | **2b**: X = Br, R = 4-Me | 71 |
| 8 | **1f** | **2c**: X = Br, R = 4-*t*-Bu | 60 |
| 9 | **1f** | **2d**: X = Br, R = 3-Me | 52 |
| 10 | **1f** | **2e**: X = Cl, R = H | 0 |

**Table 2** (*continued*)

| Entry | Thioamide (**1**) | ArX (**2**) | Yield[b] (%) |
|---|---|---|---|
| 11 | **1f** |  **2f** | 66 |
| 12 | **1f** |  **2g** | 51 |
| 13 |  **1g** | **2a** | 55 |
| 14 |  **1h** | **2b** | 67 |

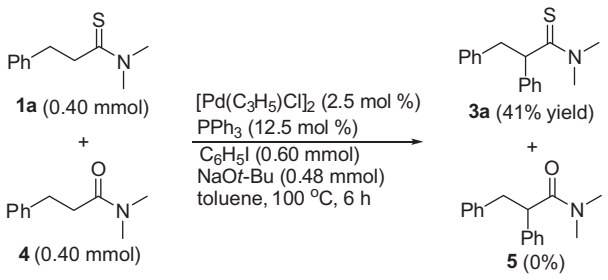
[a] All the reactions were carried out with thioamide **1** (0.40 mmol), haloarene (**2**) (0.60 mmol), NaO*t*-Bu (0.48 mmol), $[Pd(C_3H_5)Cl]_2$ (0.010 mmol), and $PPh_3$ (0.050 mmol) in toluene (2 mL) at 100 °C for 6 h unless otherwise stated. For entries 1 and 2, iodobenzene (**2a**) (1.0 mmol) was used.
[b] The isolated yield was based on thioamide **1**.

reaction conditions possibly due to the steric hindrance of the substrate.

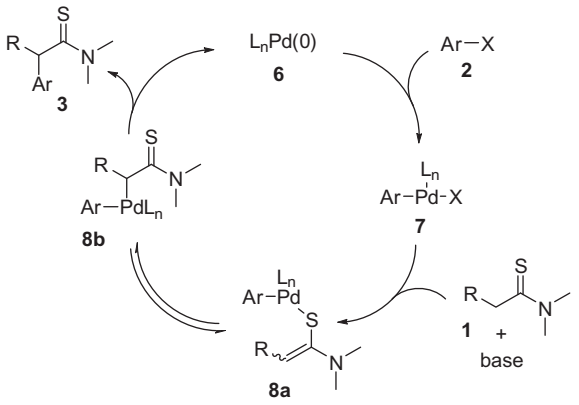
Competition experiment between thioamide **1a** and the structurally related amide **4** was carried out for the Pd-catalyzed α-arylation (Scheme 2). The arylation highly selectively occurred on thioamide **1a**, giving α-phenyl thioamide **3a** in 41% yield.[15] The high chemoselectivity for thioamide over amide observed in the experiment is probably due to the higher α-H acidity and/or the better coordination capability of thioamide **1a** than amide **4**.

While a precise reaction mechanism awaits further studies, a plausible catalytic cycle is proposed in Scheme 3. Active catalyst Pd(0) complex **6** inserts into the C–X bond of haloarene **2** to form ArPd(II)X species **7**. Compound **7** reacts with thioamide **1** under basic conditions to give a mixture of S–Pd complex **8a** and C–Pd complex **8b**, which are likely in equilibrium under the reaction conditions. C–Pd complex **8b** undergoes reductive elimination to form α-arylation product **3** and regenerate the Pd(0) catalyst **6**, completing the catalytic cycle.

In summary, this is the first report on Pd-catalyzed α-arylation of thioamides,[16–19] which has demonstrated the feasibility of the application of thioamides in coupling chemistry. Various α-aryl thioamides were prepared in moderate to good yields by the Pd-catalyzed α-arylation. The current coupling process provides




**Scheme 2.** Competition experiment between thioamide **1a** and the related amide **4** for Pd-catalyzed α-arylation.




**Scheme 3.** Proposed reaction mechanism for Pd-catalyzed α-arylation of thioamides.

an alternative synthetic method of functionalized thioamides which are present in many chemically and biologically important molecules.[1d,20–23] Moreover, this work presents a new synthetic transformation of thioamides, which might expand the applications of thioamides in organic synthesis.[1,2] Further studies on detailed reaction mechanism, substrate scope, catalyst development as well as asymmetric processes are currently underway.

## Acknowledgments

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## Supplementary data

Supplementary data (the procedure of the Pd-catalyzed α-arylation of thioamides and the characterization of the α-arylated thioamides **3** along with the $^{1}H$ and $^{13}C$ NMR spectra of **3**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.114.

## References and notes

1. For selected reviews on thioamides, see: (a) Jagodziński, T. S. *Chem. Rev.* **2003**, *103*, 197; (b) Danilkina, N. A.; Mikhailov, L. E.; Ivin, B. A. *Russian J. Org. Chem.* **2006**, *42*, 783; (c) Murai, T. *Pure Appl. Chem.* **2010**, *82*, 541; (d) Banala, S.; Süssmuth, R. D. *ChemBioChem* **2010**, *11*, 1335.
2. For selected references on applications of thioamides in total synthesis, see: (a) Fang, F. G.; Maier, M. E.; Danishefsky, S. J.; Schulte, G. *J. Org. Chem.* **1990**, *55*, 831; (b) Nicolaou, K. C.; Lizos, D. E.; Kim, D. W.; Schlawe, D.; de Noronha, R. G.; Longbottom, D. A.; Rodriquez, M.; Bucci, M.; Cirino, G. *J. Am. Chem. Soc.* **2006**, *128*, 4460; (c) Nicolaou, K. C.; Dethe, D. H.; Chen, D. Y.-K. *Chem. Commun.* **2008**, 2632; (d) Padwa, A.; Beall, L. S.; Heidelbaugh, T. M.; Liu, B.; Sheehan, S. M. *J. Org. Chem.* **2000**, *65*, 2684; (e) Xie, J.; Okano, A.; Pierce, J. G.; James, R. C.; Stamm, S.; Crane, C. M.; Boger, D. L. *J. Am. Chem. Soc.* **2012**, *134*, 1284.
3. For leading references on reactions of thioacetylamide with iodoarenes, see: (a) Murguía, M. C.; Rossi, R. A. *Tetrahedron Lett.* **1997**, *38*, 1355; (b) Murguía, M. C.; Ricci, C. G.; Cabrera, M. I.; Luna, J. A.; Grau, R. J. *J. Mol. Catal. A Chem.* **2001**, *165*, 113.
4. For leading references on thioamides serving as C-nucleophiles in asymmetric Aldol reactions, see: (a) Suzuki, Y.; Yazaki, R.; Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 5026; (b) Iwata, M.; Yazaki, R.; Suzuki, Y.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 18244; (c) Iwata, M.; Yazaki, R.; Chen, I.-H.; Sureshkumar, D.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2011**, *133*, 5554.
5. For selected reviews on transition-metal-catalyzed α-arylation of carbonyl and related compounds, see: (a) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234; (b) Shao, Z.-H.; Zhang, H.-B. *Youji Huaxue* **2005**, *25*, 282; (c) Burtoloso, A. C. B. *Synlett* **2009**, 320; (d) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676.
6. For selected references on transition-metal-catalyzed α-arylation of amides, see: (a) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402; (b) Hama, T.; Liu, X.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 11176; (c) Hama, T.; Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 4976; (d) Altman, R. A.; Hyde, A. M.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 9613; (e) Durbin, M. J.; Willis, M. C. *Org. Lett.* **2008**, *10*, 1413; (f) Taylor, A. M.; Altman, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 9900.
7. (a) Hlavinka, M. L.; Greco, J. F.; Hagadorn, J. R. *Chem. Commun.* **2005**, 5304; (b) Bordwell, F. G.; Fried, H. F. *J. Org. Chem.* **1991**, *56*, 4218.
8. Guziec, F. S., Jr; Wasmund, L. M. *Tetrahedron Lett.* **1990**, *31*, 23.
9. Cronyn, M. W.; Goodrich, J. E. *J. Am. Chem. Soc.* **1952**, *74*, 3936.
10. Masuda, R.; Hojo, M.; Ichi, T.; Sasano, S.; Kobayashi, T.; Kuroda, C. *Tetrahedron Lett.* **1991**, *32*, 1195.
11. Lehmann, J.; Linden, A.; Heimgartner, H. *Helv. Chim. Acta* **1999**, *82*, 888.
12. Harrowven, D. C.; Lucas, M. C.; Howes, P. D. *Tetrahedron* **1999**, *55*, 1187.
13. Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 10275.
14. Some unidentified by-products were formed in the Pd(0)-catalyzed α-arylation of *N*,*N*-dimethyl-3-phenylpropanethioamide (**1a**) with iodobenzene (**2a**) (Table 2, entry 1) as judged by $^{1}H$ NMR spectroscopy of the crude reaction mixture.
15. The corresponding α-arylation product of amide (**5**) was not isolated in the competition experiment.
16. For selected references on synthesis of thiamides by using Lawesson reagent or $P_2O_5$, see: (a) Perregaard, J.; Scheibye, S.; Meyer, H. J.; Thomsen, I.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1977**, *86*, 679; (b) Kaleta, Z.; Makowski, B. T.; Soós, T.; Dembinski, R. *Org. Lett.* **2006**, *8*, 1625; (c) Bibian, M.; Martinez, J.; Fehrentz, J.-A. *Tetrahedron* **2011**, *67*, 7042; (d) Hrobarik, P.; Hrobarikova, V.; Sigmundova, I.; Zahradnik, P.; Fakis, M.; Polyzos, I.; Persephonis, P. *J. Org. Chem.* **2011**, *76*, 8726; (e) Yazaki, R.; Kumagai, N.; Shibasaki, M. *Org. Lett.* **2011**, *13*, 952.
17. For selected references on synthesis of thiamides via Willgerodt–Kindler reaction, see: (a) Kindler, K. *Liebigs Ann. Chem.* **1923**, *431*, 187; (b) Brown, E. V. *Synthesis* **1975**, 358; (c) Zbruyev, O. I.; Stiasni, N.; Kappe, C. O. *J. Comb. Chem.* **2003**, *5*, 145; (d) Kapanda, C. N.; Muccioli, G. G.; Labar, G.; Draoui, N.; Lambert, D. M.; Poupaert, J. H. *Med. Chem. Res.* **2009**, *18*, 243.
18. For selected references on synthesis of thiamides via condensation of dithioates with amines, see: (a) Kornfeld, E. C. *J. Org. Chem.* **1951**, *16*, 131; (b) Lawson, A.; Searle, C. E. *J. Chem. Soc.* **1957**, 1556; (c) Abrunhosa, I.; Gulea, M.; Levillain, J.; Masson, S. *Tetrahedron: Asymmetry* **2001**, *12*, 2851; (d) Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 16464; (e) Mercey, G.; Lohier, J.-F.; Gaumont, A.-C.; Levillain, J.; Gulea, M. *Eur. J. Org. Chem.* **2009**, 4357.
19. For selected references on synthesis of thiamides via addition of $H_2S$ to nitriles, see: (a) Ralston, A. W.; Vander Wal, R. J.; McCorkle, M. R. *J. Org. Chem.* **1939**, *4*, 68; (b) Gardner, T. S.; Wenis, E.; Lee, J. *J. Org. Chem.* **1954**, *19*, 753; (c) Spychala, J. *J. Sulfur Chem.* **2006**, *27*, 203; (d) Täeuscher, E.; Calderón-Ortiz, L.; Weiβ, D.; Beckert, R.; Görls, H. *Synthesis* **2011**, 2334.
20. For selected references on biologically active thioamide compounds, see: (a) Zacharie, B.; Lagraoui, M.; Dimarco, M.; Penney, C. L.; Gagnon, L. *J. Med. Chem.* **1999**, *42*, 2046; (b) Miwa, J. H.; Patel, A. K.; Vivatrat, N.; Popek, S. M.; Meyer, A. M. *Org. Lett.* **2001**, *3*, 3373; (c) Gannon, M. K., II; Holt, J. J.; Bennett, S. M.; Wetzel, B. R.; Loo, T. W.; Bartlett, M. C.; Clarke, D. M.; Sawada, G. A.; Higgins, J. W.; Tombline, G.; Raub, T. J.; Detty, M. R. *J. Med. Chem.* **2009**, *52*, 3328; (d) Agrawal, A.; de Oliveira, C. A. F.; Cheng, Y.; Jacobsen, J. A.; McCammon, J. A.; Cohen, S. M. *J. Med. Chem.* **2009**, *52*, 1063.
21. For selected references on applications of thioamides in asymmetric catalysis, see: (a) Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 16464; (b) Geng, X.-L.; Wang, J.; Li, G.-X.; Chen, P.; Tian, S.-F.; Qu, J. *J. Org. Chem.* **2008**, *73*, 8558; (c) Cao, J.-L.; Qu, J. *J. Org. Chem.* **2010**, *75*, 3663.
22. For selected references on applications of thioamides in coordination chemistry, see: (a) Ozturk, I. I.; Hadjikakou, S. K.; Hadjiliadis, N.; Kourkoumelis, N.; Kubicki, M.; Tasiopoulos, A. J.; Scleiman, H.; Barsan, M. M.; Butler, I. S.; Balzarini, J. *Inorg. Chem.* **2009**, *48*, 2233; (b) Wang, Q.-Q.; Begum, R. A.; Day, V. W.; Bowman-James, K. *Inorg. Chem.* **2012**, *51*, 760.
23. For selected references on applications of thioamides in material science, see: (a) Song, K. C.; Kim, J. S.; Park, S. M.; Chung, K.-C.; Ahn, S.; Chang, S.-K. *Org. Lett.* **2006**, *8*, 3413; (b) Goldberg, J. M.; Batjargal, S.; Petersson, E. J. *J. Am. Chem. Soc.* **2010**, *132*, 14718; (c) Okamoto, K.; Yamamoto, T.; Akita, M.; Wada, A.; Kanbara, T. *Organometallics* **2009**, *28*, 3307; (d) Fanous, J.; Wegner, M.; Grimminger, J.; Andresen, Ä.; Buchmeiser, M. R. *Chem. Mater.* **2011**, *23*, 5024; (e) Mason, C. R.; Maynard-Atem, L.; Al-Harbi, N. M.; Budd, P. M.; Bernardo, P.; Bazzarelli, F.; Clarizia, G.; Jansen, J. C. *Macromolecules* **2011**, *44*, 6471.