Tetrahedron Letters 56 (2015) 595–598

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

# Pd-catalyzed asymmetric α-allylic alkylation of thioamides

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ARTICLE INFO

*Article history:*
Received 9 September 2014
Revised 29 November 2014
Accepted 8 December 2014
Available online 13 December 2014

*Keywords:*
Allylic alkylation
Thioamide
Asymmetric
Palladium
Catalysis

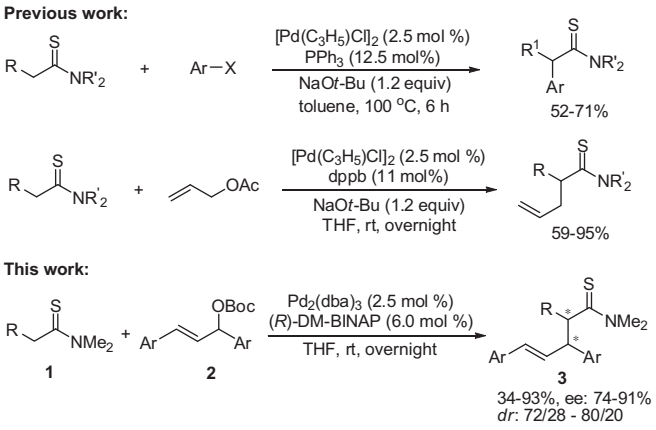
ABSTRACT

This Letter describes the first catalytic asymmetric α-allylic alkylation of thioamides. By using 5 mol % Pd-(*R*)-DM-BINAP complex as the chiral catalyst, various thioamides were efficiently α-allylic alkylated with 1,3-diarylallyl carbonates under mild conditions, affording a variety of α-substituted thioamides in good yields with high enantioselectivity and moderate diastereoselectivity. This work represents a useful and direct route to prepare chiral functionalized thioamides.



Thioamides[1] are important compounds with wide applications in organic synthesis,[2] catalysis,[3] material chemistry,[4] and medicinal chemistry.[5] Thioamides have more acidic α-protons than the corresponding amides[6] and thus have been extensively employed as carbon nucleophiles in organic synthesis.[1,2] However, the application of thioamides as carbon nucleophiles in transition-metal-catalyzed C–C coupling with various electrophiles are rarely investigated.[7,8] Recently, we have shown that thioamides were reactive substrates for Pd-catalyzed α-arylation[8a] and allylic alkylation[8b] (Scheme 1), providing two efficient methods for the synthesis of α-functionalized thioamides. In the further studies, we have found that Pd-catalyzed asymmetric allylic alkylation of thioamides **1** can be realized by using *tert*-butyl 1,3-diarylallyl carbonates **2** as allylic electrophiles and (*R*)-(+)-2,2′-bis[di(3,5-xylyl)phosphine]-1,1′-binaphthyl [(*R*)-DM-BINAP] as chiral ligand, to give a variety of chiral α-branched thioamides **3** in good yields with high enantioselectivity (Scheme 1).[9–11] Herein, we wish to report our studies on the catalytic asymmetric allylic alkylation of thioamides.

The studies commenced with the investigation of the impact of chiral ligands on Pd-catalyzed allylic alkylation of *N*,*N*-dimethyl octanethioamide (**1a**) with 1,3-diphenylallylic acetate (**2a**) (Scheme 2). Bidentate P–P (**L1**–**5**)[12a–f] and N–P (**L6**)[12g,h] ligands were both active for the reaction. The chiral ligands had a significant influence on the reaction in terms of diastereo- and enantioselectivities. Phosphine ligands **L1**–**5** exhibited low to moderate diastereoselectivity in the reaction, nevertheless, up to 92:8 *dr* value was obtained with N–P ligand **L6**. The distinct difference in diastereoselectivity among the chiral ligands **L1**–**6** suggested that the catalyst has thrown a crucial impact on the diastereoselectivity and also implied that potential epimerization was likely not severe although strong base NaO*t*-Bu was employed. It was supposed that the thioamide **1a** had been converted into thio-enolate by the equivalent base NaO*t*-Bu to serve as the active nucleophile in the Pd(0)-catalyzed allylic alkylation. This would greatly lower the basicity of the reaction mixture, thus no obvious epimerization




**Scheme 1.** Pd-catalyzed α-arylation and allylic alkylation of thioamides.

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† The authors contributed equally to this work and share first authorship.

http://dx.doi.org/10.1016/j.tetlet.2014.12.031
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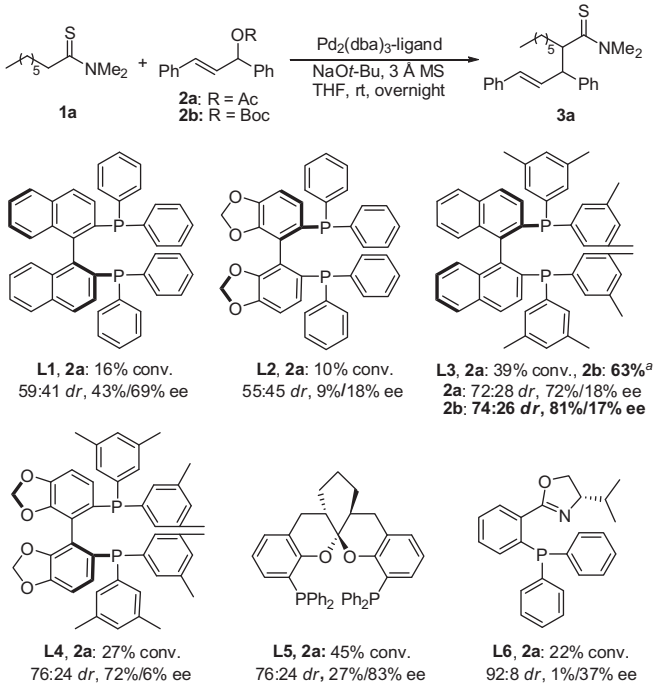


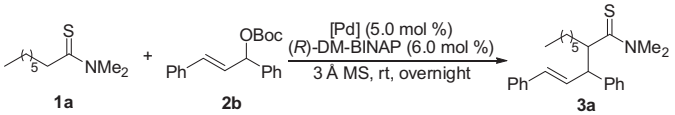

**Scheme 2.** Screening ligands for the Pd catalyzed asymmetric α-allylic alkylation of thioamides. All the reactions were carried out with thioamide **1a** (0.10 mmol), **2** (0.15 mmol), NaO*t*-Bu (0.10 mmol), $Pd_2(dba)_3$ (0.0025 mmol), ligand (0.0060 mmol), and 3 Å molecular sieves (0.020 g) in dry THF (0.60 mL) under $N_2$ atmosphere at room temperature overnight unless otherwise stated. For the reaction using **L4** as the ligand, thioamide **1a** (0.061 mmol), allylic ester **2a** (0.079 mmol), NaO*t*-Bu (0.078 mmol), $Pd_2(dba)_3$ (0.0018 mmol) and **L4** (0.0078 mmol) were used. The conversions were based on **1a** and determined by $^1$H NMR analysis of the crude reaction mixtures, the *dr* values were also determined by $^1$H NMR analysis of the crude reaction mixtures and the ee's were determined by chiral HPLC analysis; [a]Isolated yield based on **1a**.

was observed in the ligand-screening experiments. Biaryl phosphine ligands DM-BINAP (**L3**) and DM-SEGPHOS (**L4**) showed the highest enantioselectivity (72% ee) for the major diastereoisomer, however, spiroketal bisphosphine (SKP) (**L5**) was most enantioselective (83% ee) for the minor diastereoisomer in the reaction. The *O*-activating group of the allylic electrophiles **2** has also been explored for the Pd-catalyzed allylic alkylation of thioamide **1a** using DM-BINAP (**L3**) as the chiral ligand. *O*-Boc-protected allylic carbonate **2b** displayed higher reactivity (63% isolated yield vs 39% conversion) and better enantioselectivity (ee: 81% vs 72%) than the *O*-Ac-protected allylic ester **2a**. Thus, we chose (*R*)-DM-BINAP (**L3**) as the chiral ligand and *O*-Boc-protected allylic carbonates as allylic electrophiles in the following studies.

Reaction parameters including base, palladium source, and solvent were then investigated in the Pd-catalyzed asymmetric allylic alkylation of thioamide **1a** with carbonate **2b** using (*R*)-DM-BINAP (**L3**) as the chiral ligand (Table 1). In order to remove the α-H of thioamide **1a**, strong base was necessary for the reaction. For example, NaO*t*-Bu promoted the allylic alkylation smoothly (Table 1, entry 1), while $Cs_2CO_3$ was inactive for the reaction (Table 1, entry 2). All the strong bases examined displayed similar performance in terms of diastereo- and enantioselectivities (Table 2, entries 1 and 3–5). NaHMDS was chosen as the base for the reaction. Further studies revealed that $Pd_2(dba)_3$ was the suitable palladium precursor (Table 1, entries 4 and 6–8) and THF was the solvent of choice for the asymmetry α-allylic alkylation of thioamides (Table 1, entries 4 and 9–10).

Under the above established optimal conditions, substrate scope was then tested for the Pd-catalyzed asymmetric α-allylic

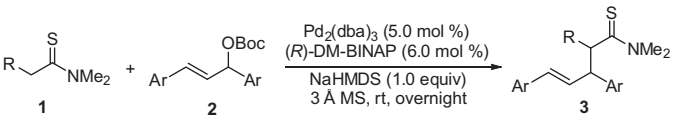
**Table 1**
Optimization of reaction conditions for the Pd-catalyzed asymmetric α-allylic alkylation of thioamides[a]

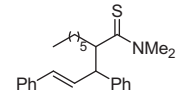
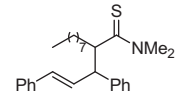
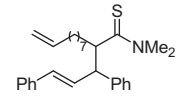
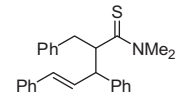
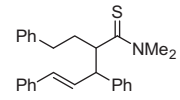
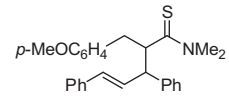



| Entry | Conditions | Yield[b] (%) | *dr*[c] | ee[d] (%) |
|---|---|---|---|---|
| 1 | NaO*t*-Bu, $Pd_2(dba)_3$, THF | 63 | 74:26 | 81/17 |
| 2 | $Cs_2CO_3$, $Pd_2(dba)_3$, THF | —[e] | | |
| 3 | LiHMDS, $Pd_2(dba)_3$, THF | 78 | 73:27 | 87/12 |
| 4 | NaHMDS, $Pd_2(dba)_3$, THF | 77 | 75:25 | 88/19 |
| 5 | KHMDS, $Pd_2(dba)_3$, THF | 77 | 72:28 | 88/26 |
| 6 | NaHMDS, $Pd(OAc)_2$, THF | 55 | 77:23 | 84/17 |
| 7 | NaHMDS, $PdCl_2$, THF | 50 | 76:24 | 87/18 |
| 8 | NaHMDS, $[Pd(C_3H_5)Cl]_2$, THF | 59 | 76:24 | 82/17 |
| 9 | NaHMDS, $Pd_2(dba)_3$, DCM | —[e] | | |
| 10 | NaHMDS, $Pd_2(dba)_3$, toluene | 55 | 76:24 | 74/22 |

[a] All the reactions were carried out with thioamide **1a** (0.10 mmol), allylic carbonate **2b** (0.15 mmol), base (0.10 mmol), [Pd] (0.0050 mmol), (*R*)-DM-BINAP(0.0060 mmol) and 3 Å molecular sieves (0.020 g) in the solvent (0.60 mL) under $N_2$ atmosphere at room temperature overnight.
[b] Isolated yields based on **1a**.
[c] The *dr* values were determined by $^1$H NMR analysis of the crude reaction mixtures.
[d] The ee's were determined by chiral HPLC analysis.
[e] No alkylation product **3a** was observed as judged by $^1$H NMR analysis of the crude reaction mixture.

**Table 2**
Pd-catalyzed asymmetric α-allylic alkylation of thioamides[a]




| Entry | Product | Yield[b] (%) | *dr*[c] | ee[d] (%) |
|---|---|---|---|---|
| 1 |  **3a** | 77 | 75:25 | 88/19 |
| 2 |  **3b** | 76 | 74:26 | 90/19 |
| 3 |  **3c** | 69 | 74:26 | 89/26 |
| 4 |  **3d** | 93 | 77:23 | 91/26 |
| 5 |  **3e** | 90 | 72:28 | 87/14 |
| 6 |  **3f** | 84 | 76:24 | 87/13[e] |