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Catalytic dehydrogenative *N*-((triisopropylsilyl)oxy)carbonyl (Tsoc) protection of amines using iPr<sub>3</sub>SiH and CO<sub>2</sub><sup>+</sup>

S. Tanaka, T. Yamamura, S. Nakane and M. Kitamura\*

A versatile method has been found to catalyze the dehydrogenative N-((triisopropylsilyl)oxy)carbonyl (Tsoc) protection of amines using Pd/C, volatile iPr<sub>3</sub>SiH and CO<sub>2</sub> gas without the liberation of any salts. A simple filtration/evaporation process facilitates the easy isolation of the product, thereby enhancing the utility of Tsoc as an amine-protecting group in organic synthesis.

((Triisopropylsilyl)oxy)carbonyl (Tsoc) group reported by Lipshutz in 1999<sup>1</sup> is an excellent protecting group for amines. N-Tsoc-protected amines are stable under the conditions of TFA/CH<sub>2</sub>Cl<sub>2</sub>, H<sub>2</sub>/Pd-C, and morpholine/DMF used for the removal of Boc, Cbz, and Fmoc protecting groups, respectively, while Tsoc is easily removed under the conditions of TBAF/THF.<sup>2</sup> The orthogonality of Tsoc toward these protecting groups, as well as its easy detachment process, is attractive. Furthermore, silvl carbamates can be used both as intermediates for the synthesis of organic carbamates<sup>3,4</sup> and more substituted amines,<sup>5</sup> and as linkers in solid-phase combinatorial chemistry.<sup>3</sup> Scheme 1 summarizes the methods reported for installing Tsoc on primary and secondary amines 1 to obtain N-Tsoc amines 2, namely, (i) insertion of CO<sub>2</sub> into the N-Si bond of silvl amides;<sup>6</sup> (ii) silvlation of ammonium carbamates;<sup>1,7</sup> and (iii) alkyl/silyl carbamate exchange.8 However, these multistep or "salt-liberation-type" constructions of N-Tsoc amines have low atom- and step-economies, as well as they lack operational simplicity, which limits their practical utility and generality. Herein, we have focused on a direct and constructive process without salt liberation (iv, Scheme 1), in which 1, iPr<sub>3</sub>SiH, and CO<sub>2</sub> are converted to 2 under the influence of a heterogeneous catalyst. The only co-product is H2. Simple filtration/evaporation of the reaction mixture gives 2, which is uncontaminated by catalyst, unlike in a homogeneous system.9



Scheme 1 Conventional and new approaches to *N*-Tsoc-protected amines.

With a focus on commercially available heterogeneous metal catalysts, the reactivity was investigated in the reaction of benzyl amine (**1a**) with iPr<sub>3</sub>SiH under the standard conditions of 100 mM **1a**, 100 mM iPr<sub>3</sub>SiH, 1 atm CO<sub>2</sub>, 5 mol% catalyst (metal equivalent), and DMA at 50 °C for 16 h. Representative results are shown in Fig. 1.<sup>10</sup> The Pd catalysts tested showed more or less reactivity depending on the type or method of support, or the Pd source. Among them, 10 wt% Pd on dry matrix carbon (Aldrich 520888) showed the highest reactivity in realizing the quantitative conversion of **1a** to **2a** (red bar). No reactivity was observed with Fe, RANEY<sup>®</sup> Ni, Ru/C, Rh/C, Pt/C, or PtO<sub>2</sub>.

Table 1 summarizes the results of optimization. DMA,  $CH_3CN$ , and  $C_2H_5CN$  were the solvents of choice (entries 1–3). In DMF, *N*-formylation of **1a** occurred (entry 4). With the particular standard substrate tested (**1a**), *N*-Tsoc-protected dibenzylamine was produced in 5% yield in  $CH_3CN$  (entry 2). In THF and *t*-BuOH, the reaction proceeded slowly (entries 5 and 6), and no reaction occurred in CPME, dioxane,  $CH_2Cl_2$ , benzene, or hexane under the standard conditions (entries 7–11). The reactivity was enhanced by increasing the pressure of  $CO_2$  and/or the reaction temperature within the range of 1–10 atm and 25–100 °C, respectively. At 25 °C, the reactivity was slow. At 10 atm of  $CO_2$  and 50 °C, the reaction was completed within 6 h, and the time was halved at 100 °C (entries 12–14). The catalyst loading could be reduced to 2 mol% with completion within a tolerable time range (entry 15). One mol of iPr<sub>3</sub>SiH was enough to attain a



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Graduate School of Pharmaceutical Sciences, Graduate School of Science, and Research Center for Materials Science, Nagoya University, Chikusa, Nagoya 464-8601, Japan. E-mail: kitamura@os.rcms.nagoya-u.ac.jp

<sup>†</sup> Electronic supplementary information (ESI) available: Details of the general procedure for Tsoc protection, and NMR spectral data of the substrates and products. See DOI: 10.1039/c5cc04594k



**Fig. 1** Screening of heterogeneous metal catalysts. <sup>*a*</sup> 10 wt% loading, matrix carbon, dry support. <sup>*b*</sup> 5 wt% loading, matrix carbon powder, wet support. <sup>*c*</sup> 10 wt% loading, matrix activated carbon support. <sup>*d*</sup> 5 wt% reduced. <sup>*e*</sup> Reduced, 5 wt% loading.

Table 1Dehydrogenative protection of benzylamine (1a) as the N-((tri-<br/>organosilyl)oxy)carbamates using triorganosilane and CO2 in the presence<br/>of 10 wt% Pd on dry matrix carbon (Aldrich 520888)<sup>a</sup>

| Entry           | Solvent            | $CO_2$ (atm) | Temp. (°C) | Silane                 | Time (h) | $\operatorname{Yield}^{b}(\%)$ |
|-----------------|--------------------|--------------|------------|------------------------|----------|--------------------------------|
| 1               | DMA                | 1            | 50         | iPr <sub>3</sub> SiH   | 16       | >99                            |
| 2               | CH <sub>3</sub> CN | 1            | 50         | iPr <sub>3</sub> SiH   | 16       | 91 <sup>c</sup>                |
| 3               | $C_2H_5CN$         | 1            | 50         | iPr <sub>3</sub> SiH   | 16       | 87 <sup>c</sup>                |
| 4               | DMF                | 1            | 50         | iPr <sub>3</sub> SiH   | 16       | $86^{c,d}$                     |
| 5               | THF                | 1            | 50         | iPr <sub>3</sub> SiH   | 16       | 91                             |
| 6               | t-BuOH             | 1            | 50         | iPr <sub>3</sub> SiH   | 16       | 98                             |
| 7               | CPME               | 1            | 50         | iPr <sub>3</sub> SiH   | 16       | <1                             |
| 8               | Dioxane            | 1            | 50         | iPr <sub>3</sub> SiH   | 16       | <1                             |
| 9               | $CH_2Cl_2$         | 1            | 50         | iPr <sub>3</sub> SiH   | 16       | <1                             |
| 10              | Benzene            | 1            | 50         | iPr <sub>3</sub> SiH   | 16       | <1                             |
| 11              | Hexane             | 1            | 50         | iPr <sub>3</sub> SiH   | 16       | <1                             |
| 12              | DMA                | 10           | 50         | iPr <sub>3</sub> SiH   | 6        | >99                            |
| 13              | DMA                | 1            | 25         | iPr <sub>3</sub> SiH   | 16       | 90                             |
| 14              | DMA                | 10           | 100        | iPr <sub>3</sub> SiH   | 3        | >99                            |
| $15^e$          | DMA                | 1            | 50         | iPr <sub>3</sub> SiH   | 32       | >99                            |
| 16 <sup>f</sup> | DMA                | 1            | 50         | iPr <sub>3</sub> SiH   | 6        | >99                            |
| 17 <sup>f</sup> | CH <sub>3</sub> CN | 10           | 50         | Et <sub>3</sub> SiH    | 16       | 92 <sup>c</sup>                |
| $18^{f}$        | CH <sub>3</sub> CN | 10           | 50         | Ph <sub>2</sub> tBuSiH | 16       | 95 <sup>c</sup>                |

<sup>*a*</sup> Conditions: 0.2 mmol scale, **[1a]** = 100 mM 5 mol% Pd/C (metal equivalent). <sup>*b*</sup> Determined by <sup>1</sup>H NMR analysis. <sup>*c*</sup> *N*-Tsoc-protected dibenzylamine was produced in 5%–10% yield. (*S*)-Phenylalanine methyl ester (**1i**) was quantitatively converted to the corresponding silyl carbamate. <sup>10</sup> See Table 2. <sup>*d*</sup> *N*-Formylbenzylamine was obtained in 9%. <sup>*e*</sup> 2 mol% of Pd/C. <sup>*f*</sup> 2.5 mol amt of silane.

quantitative conversion, but 2.5 mol of  $iPr_3SiH$  shortened the reaction time to 6 h (entry 16). Even with an excess amount of  $iPr_3SiH$ , the synthetic utility was not reduced because of the high volatility of  $iPr_3SiH$ . Et<sub>3</sub>SiH and  $Ph_2tBuSiH$  could also be used to obtain the corresponding silyl carbamates in high yield (entries 17 and 18).

The reliability of the new Tsoc installation method was confirmed using 50 mmol of 1a (entry 1 in Table 2). This large-scale reaction



<sup>*a*</sup> The reaction was carried out using 100 mM **1** in DMA on a 0.2 mmol scale for 16 h, and the yield was determined after isolation unless otherwise specified. <sup>*b*</sup> [iPr<sub>3</sub>SiH] = 100 mM, 5 mol% of Pd/C, 1 atm CO<sub>2</sub>, 50 °C. <sup>*c*</sup> 50 mmol scale. [substrate] = [iPr<sub>3</sub>SiH] = 500 mM. <sup>*d*</sup> A Tedlar<sup>®</sup> bag was used for supplying 1 atm CO<sub>2</sub> gas. <sup>*e*</sup> [iPr<sub>3</sub>SiH] = 250 mM, 10 mol% Pd/C, 10 atm CO<sub>2</sub>, 100 °C. <sup>*f*</sup> [iPr<sub>3</sub>SiH] = 250 mM, 10 mol% Pd/C, 1 atm CO<sub>2</sub>, 50 °C. <sup>*s*</sup> [iPr<sub>3</sub>SiH] = 1250 mM, 5 mol% Pd/C, 1 atm CO<sub>2</sub>, 50 °C. <sup>*f*</sup> No racemization.<sup>10</sup> <sup>*i*</sup> [Et<sub>3</sub>SiH] = 250 mM, 5 mol% Pd/C, 10 atm CO<sub>2</sub>, 50 °C. <sup>*i*</sup> 32 h.

using a Tedlar<sup>®</sup> bag to supply 1 atm of CO<sub>2</sub> gas afforded **2a** in 98% isolated yield, confirming the operational simplicity. The ICP analysis of the product indicated that contamination with Pd was <1 ppb.<sup>10</sup> The applicability of the new Tsoc installation method to other amines is provided in Table 2. Primary, secondary, and tertiary alkyl amines could be used (entries 1–5); however, aromatic amines could not be used (entries 6–8). Various  $\alpha$ -amino esters protected by Tsoc were quantitatively prepared (entries 9–14). The isolated yields were very high in all the cases because of the simple filtration/evaporation workup. No racemization of (*S*)-phenylalanine methyl ester (Phe-OMe), (**1i**) was observed after the Tsoc protection of **1i** followed by deprotection (100 mM CH<sub>3</sub>CN solution of *N*-Tsoc-Phe-OMe; **1**.0 mol amount TBAF; rt; 10 min).‡<sup>10</sup>

As shown in Table 2, ester, amide, and indole NH functional groups remained intact. Reactivity was maintained even in the presence of a sulfide functional group (entry 13). In the presence of 4-phenylbutan-2-one, 3-phenylpropanenitrile, or (3,4-dimethylpent-3-en-1-yl)benzene (100 mM), **1a** (100 mM) was efficiently converted to **2a** under the standard conditions,

while these competitive substrates remained intact. Ketone, nitrile, and tetra-substituted alkene functional groups were found to be tolerated, but a disadvantage was that less-substituted alkenes were hydrosilylated. This problem could be alleviated by carrying out the reaction in the presence of sacrificial olefins such as ethene.<sup>10</sup>

In summary, a new method has been established for the catalytic dehydrogenative Tsoc protection of amines using  $iPr_3SiH$  and  $CO_2$  in the presence of a versatile 10 wt% Pd catalyst on dry matrix carbon (Aldrich 520888). The only coproduct is  $H_2$ , and both  $iPr_3SiH$  and  $CO_2$  are easily removed, making the reaction system clean. The heterogeneous process, which has high atomand step-economy, makes product isolation simple and easy. The high efficiency of the present method should enhance the utility of the Tsoc protecting group in the multistep synthesis of natural products and pharmaceuticals.

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## Notes and references

‡ Experimental: a dried and Ar-filled 1-L Young-type Schlenk flask containing a magnetic stirring bar was charged with (*S*)-phenylalanine methyl ester (1i) with an *S/R* ratio of >99.5:0.5 (10.0 g, 56.0 mmol), iPr<sub>3</sub>SiH (22.2 g, 140 mmol), and degassed DMA (112 mL). After the addition of 10 wt% Pd on dry matrix carbon (Aldrich 520888; 2.80 mmol in Pd equivalent; 5 mol% for 1i), the inlet pressure of the Schlenk tube was slightly reduced; 1 atm of CO<sub>2</sub> gas was introduced from a cylinder and the mixture was stirred for 10 min.<sup>11</sup> After the tube was sealed with

the Young tap, the mixture was vigorously stirred at 50 °C for 16 h, and then cooled to rt. Filtration through Celite (5 cm  $\phi \times 2$  cm) followed by the evaporation of the filtrate *in vacuo* gave nearly pure *N*-Tsoc-(*S*)-phenylalanine methyl ester (2i) (20.7 g, 95% yield), which contained less than 1 ppb of Pd.<sup>10</sup>

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- 10 For details, see ESI<sup>†</sup>.
- 11 The <sup>1</sup>H-NMR analysis of **1a** (*ca.* 200 mM) under 1 atm of  $CO_2$  in  $CD_3CN$  at 25 °C indicated that *ca.* 20% of **1a** was converted to the carbamate. Decreasing the temperature to 0 °C, 90% of **1a** was consumed, while little formation of the carbamate was observed at 80 °C.