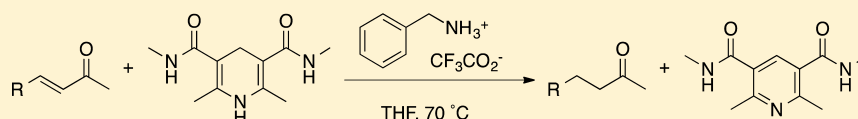


# A Hantzsch Amido Dihydropyridine as a Transfer Hydrogenation Reagent for $\alpha,\beta$ -Unsaturated Ketones

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**S** Supporting Information



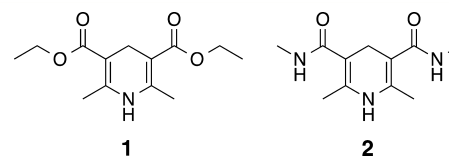
**ABSTRACT:** An improved synthesis of the bis-methylamido Hantzsch dihydropyridine is described. The Hantzsch amide is demonstrated to be an effective transfer hydrogenation reagent using  $\alpha,\beta$ -unsaturated ketones as the test case. Unreacted Hantzsch amide and the bis-methylamidopyridine byproduct are effectively removed by extraction in contrast to the commonly used Hantzsch diethyl ester. Several examples are given with the reaction being more effective for conjugated aromatic substrates than for aliphatics.

## INTRODUCTION

Addition of hydrogen to unsaturated compounds is an essential transformation in synthetic organic chemistry. While this is often very effectively accomplished through the use of metal catalysts under an atmosphere of hydrogen gas, it is frequently desirable to avoid expensive and toxic metal catalysts and the explosive nature of  $H_2$ . For these reasons, over the last several decades a significant quantity of research effort has been expended on the development of transfer hydrogenation methods that avoid such disadvantages.<sup>1–5</sup> Further avoiding metallocatalysts, the organic hydride donors have captured recent attention including benzothiazolines and related species<sup>6–13</sup> and the Hantzsch dihydropyridines.<sup>14</sup> Of course, biological systems effect transfer hydrogenation transformations via enzymes that utilize the organic hydride-donating cofactors FADH and NAD(P)H.<sup>15</sup> Not surprisingly then, the Hantzsch dihydropyridines are among the best studied and most used of the synthetic organic hydride donors stemming from their initial utility as models for the active dihydropyridine moiety in NADPH and NADH.<sup>14,16</sup> Functionalities reduced early on by Hantzsch esters (HEH) include  $\alpha,\beta$ -unsaturated aldehydes and ketones.<sup>17–22</sup>

Among the Hantzsch dihydropyridines in use for transfer hydrogenation, the Hantzsch esters (e.g., 1) have garnered the most favor among organic chemists. They are easily synthesized in good yield and have good stability.<sup>14,16,23,24</sup> The discovery by List,<sup>25</sup> MacMillan,<sup>26</sup> and others that organocatalytic chiral amines or Bronsted acids could promote the HEH asymmetric transfer hydrogenation has caused a hearty increase in the study of this process.<sup>4,27–35</sup> Most notably, a persistent and often cited problem with the use of the Hantzsch esters for preparative transfer hydrogenation is the necessity for chromatographic purification of the product. Specifically, the pyridine byproducts of the reaction are difficult to separate.<sup>9,34,36,37</sup>

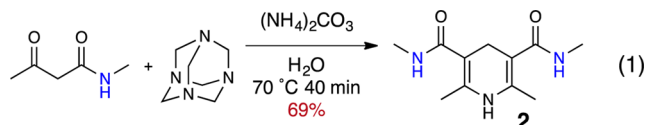
Although NADH is an amide and 1-benzyl-1,4-dihydronicotinamide has been commonly used as a model,<sup>16</sup> the symmetrical 3,5-diamido-1,4-dihydropyridines that are analogous to the



Hantzsch esters have largely been ignored as transfer hydrogenation reagents. Recent reports on the relative hydride-donating ability of various organic species including dihydropyridines hint that the diamide should be a slightly more potent hydride donor than the diester.<sup>38–42</sup> With this in mind, we have begun exploring the utility of the Hantzsch bismethylamido dihydropyridine (2,6-dimethyl-3,5-bis[(methylamino)carbonyl]-1,4-dihydropyridine, HAH 2) as a reagent for transfer hydrogenation.

## RESULTS AND DISCUSSION

The Hantzsch bismethylamide 2 was prepared by a modification of the method of Gelbard et al.<sup>43</sup> similar to that of Nomura,<sup>44</sup> resulting in a significant improvement in simplicity and yield. Gelbard's method stipulates scrupulously deaerated water as solvent and Schlenk tube filtration yielding 54% of the bismethylamide (several other Hantzsch amides were also synthesized with this method). In our improved method done in a sealed tube (eq 1), ammonium carbonate is substituted for



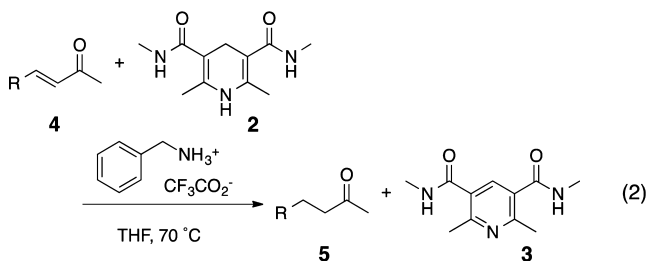
ammonium acetate, solvent water is deaerated by brief sonication alone, and the product is isolated open to the atmosphere and washed with plain deionized water. Yield is improved to 69%,

Received: January 7, 2016

Published: April 15, 2016

making the dimethylamide synthesis competitive with that of the Hantzsch ester.

The utility of the bis-methylamide has been tested in the transfer hydrogenation of a series of  $\alpha,\beta$ -unsaturated ketones according to eq 2 using benzylammonium trifluoroacetate (20



mol %) as the organocatalyst. Yields and conversions for the reaction using 2 are shown in Table 1 and are favorably competitive with those found using the HEH (1).<sup>45–47</sup> The process is more effective with conjugated aromatic  $\alpha,\beta$ -unsaturated ketones than with the aliphatic example (4i). A 50

**Table 1. Conversion and Yield for Transfer Hydrogenation of 4 (Eq 2)**

Entry	R	% Conversion	% Yield + Recovery <sup>48</sup>
a		~100	96
b		~100	94
c		97	84
d		97	86
e		~100	97
f		98	100
g		100	73
h		97	87
i		81	85
j		95	100

mol % excess of the dihydropyridine is used, and extension of the reaction time beyond 16 h does not appear to improve yields or conversions.

Percent conversion is determined by comparing specifically the integration of the terminal methyl groups of the unsaturated vs saturated ketones as shown in Figure 1 using dehydrorheosmin (4a) as the example reactant.<sup>48,49</sup> Rheosmin (“raspberry ketone”) is the principle aroma constituent of raspberries and has attracted attention recently because of its reported antiobesity activity.<sup>50–54</sup> As a test of the utility of 2 in this process, we have found that scale up of the reaction to 12 mmol of the dehydrorheosmine succeeds in giving >80% yield of the raspberry ketone without chromatography. Similar scale-up using dehydrozingerone (4b) has been accomplished in 89% yield.

Of particular importance is the relative ease of isolation of the products. As noted above, using the Hantzsch ester requires careful column chromatography for separation of the desired hydrogenation products from the pyridine byproduct. By contrast, use of the Hantzsch amide analog allows removal of the pyridine (3) through acid extraction and a short silica plug. Figure 2 shows the result of the analogous transfer hydrogenation reaction between the Hantzsch ester and dehydrorheosmin. Even after repeated aqueous acidic extraction and filtration through a silica plug, the pyridine product and unreacted dihydropyridine are not removed from the product mixture. This problem is the root of the necessity for column chromatography that is avoided with this process using HAH (2) (Figure 1). The calculated basicity of the bisamidopyridine (3) is greater than that of the analogous Hantzsch ester pyridine, and this may contribute to the observed difference in the extractability.<sup>55</sup>

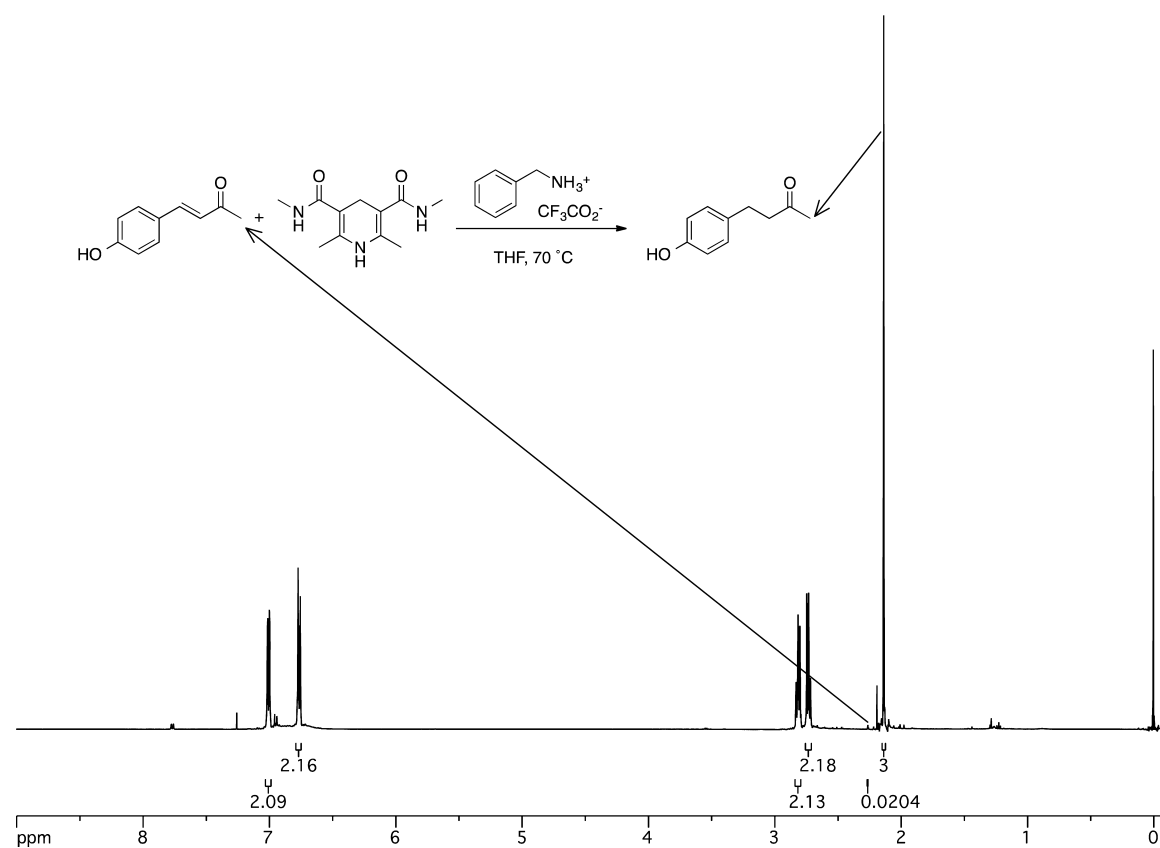
The transfer hydrogenation of 4-[(4'-dimethylamino)phenyl]-3-buten-2-one (4c) and the isolation of the reduced product provide an interesting further example of the difference between the Hantzsch ester and the amide. If the Hantzsch ester is used, then the product can be isolated in reasonable purity by acid extraction because the Hantzsch materials are not extracted under these conditions. Basification of the acidic extract and back extraction into  $\text{CH}_2\text{Cl}_2$  result in removal of most Hantzsch material.<sup>56</sup> Alternatively, reasonable results can be obtained with the Hantzsch amide by foregoing the extraction process altogether and filtering a 1:1  $\text{CH}_2\text{Cl}_2$ /hexane mixture of the reaction materials through a 1 cm plug of silica.

## CONCLUSION

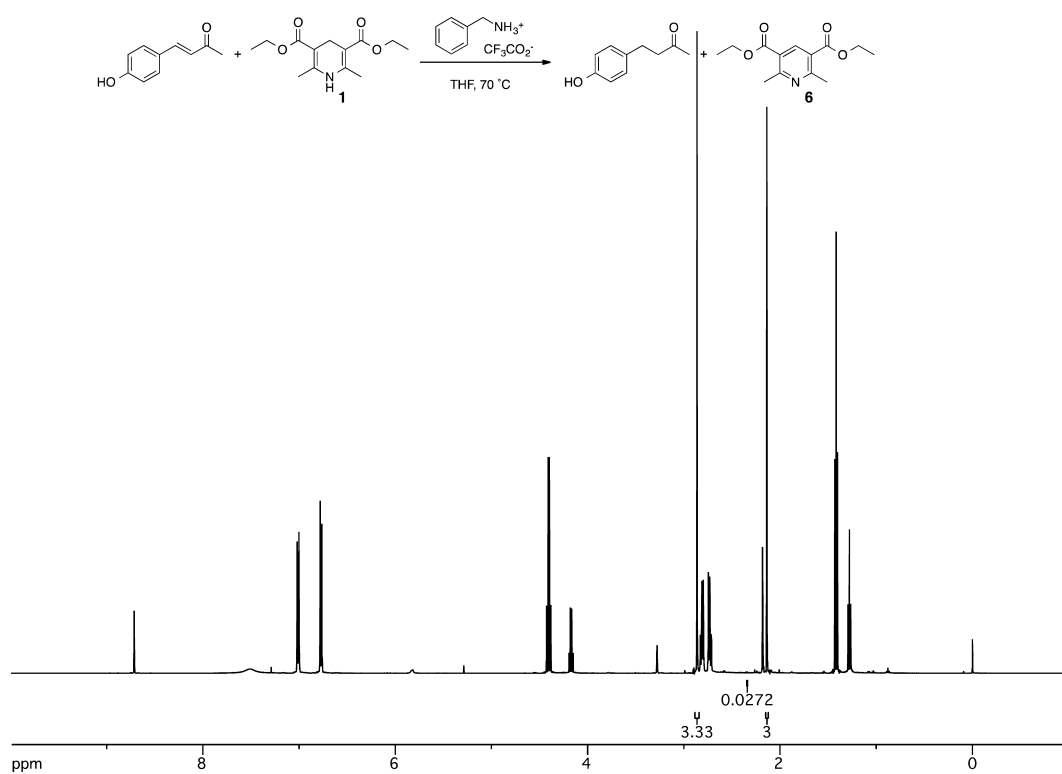
In summary, we have developed an improved synthesis of the Hantzsch amide (2) that gives higher yields under simpler conditions. We have demonstrated that this dihydropyridine can be used much as the Hantzsch ester for transfer hydrogenation with similar yields and conversions. Importantly, the difficulty of isolating hydrogenation products from the Hantzsch ester pyridine byproducts requiring column chromatography is completely overcome by the use of the Hantzsch amide. The amide itself and the pyridine byproduct can be removed easily by aqueous acidic extraction and traces further removed by filtration through a very short plug of silica. We are currently exploring additional applications of this methodology employing the Hantzsch amide.

## EXPERIMENTAL SECTION

3,4-Dihydrozingerone and 3,4-dihydrozingerone were prepared according to the method of Smith.<sup>57</sup> All other enones were commercially available and used as received or synthesized according to the method of List and match spectroscopically with literature reports.<sup>47</sup>



**Figure 1.** Extent of transfer hydrogenation of 4-(4'-hydroxyphenyl)but-3-en-2-one by Hantzsch bis-methylamide and the removal of Hantzsch materials (2 and 3) after extraction and filtration through a 0.5 cm silica plug.



**Figure 2.** Extent of transfer hydrogenation of 4-(4'-hydroxyphenyl)but-3-en-2-one by Hantzsch bis(ethyl ester) and the persistence of Hantzsch materials (1 and 6) after extraction and filtration through a 0.5 cm silica plug.

**1,4-Dihydro-2,6-dimethyl-3,5-bis[(methylamino)carbonyl]pyridine (2).** 70% *N*-methylacetamide in H<sub>2</sub>O (16 g; 96 mmol) was pipetted into a 100 mL pressure tube. To this was added hexamethylenetetramine (6.40 g; 45.7 mmol) and ammonium carbonate (5.92 g; 61.7 mmol). Deaerated (sonication) H<sub>2</sub>O was added along with a magnetic stir bar, the tube was sealed, and the mixture stirred at room temperature until all material had dissolved. The reaction tube was then placed in an oil bath at 70 °C for 1 h to give a yellow mixture and substantial precipitate. The reaction tube was removed from the oil bath, cooled to room temperature, and then cooled in an ice/water bath. Solid was collected by vacuum filtration and rinsed twice with 10 mL H<sub>2</sub>O to give a yellow solid. This was further dried under vacuum to give 7.40 g (33.2 mmol, 69.1%), mp 216–217 °C (lit 219–221 °C).<sup>43</sup> <sup>1</sup>H NMR (90.3 MHz, DMSO-*d*<sub>6</sub>) δ = 7.43 (s, 1H), 6.99 (q, *J* = 4.3 Hz, 2H), 3.08 (s, 2H), 2.62 (d, *J* = 4.5 Hz, 6H), 2.02 (s, 6H). <sup>13</sup>C NMR (22.7 MHz, DMSO-*d*<sub>6</sub>) δ = 169.0, 140.4, 99.6, 26.9, 26.3, 17.7.

**General Procedure: 4-(4'-Hydroxyphenyl)butan-2-one (Rheosmin) (5a).** 1,4-Dihydro-2,6-dimethyl-3,5-bis[(methylamino)carbonyl]pyridine (2) (168 mg; 0.757 mmol), 4-(4'-hydroxyphenyl)-3-buten-2-one (3,4-dehydorrheosmin) (81 mg; 0.50 mmol), and benzylammonium trifluoroacetate (22 mg; 0.10 mmol) were placed in a 15 mL reaction tube. To this was added a magnetic stir bar and 10 mL dry THF. The tube was sealed and heated at 70 °C for 16 h. The mixture was cooled to room temperature, and 25 mL CH<sub>2</sub>Cl<sub>2</sub> was added. This was washed with 3 M HCl (aq) (3 × 25 mL). All aqueous phases were pooled and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL). All CH<sub>2</sub>Cl<sub>2</sub> was pooled and dried over Na<sub>2</sub>SO<sub>4</sub>. The liquid was decanted off the Na<sub>2</sub>SO<sub>4</sub>, and the drying agent was rinsed with CH<sub>2</sub>Cl<sub>2</sub> (2 × 10 mL). All CH<sub>2</sub>Cl<sub>2</sub> was pooled, and the solvent removed by rotary evaporation to give a straw colored oil. This was dissolved in 3 mL CH<sub>2</sub>Cl<sub>2</sub>/hexane (1:1) and filtered through a 0.5 cm plug of silica. The silica was rinsed further with 40 mL CH<sub>2</sub>Cl<sub>2</sub>/hexane (1:1). All of the filtrate was pooled and evaporated to a slightly straw colored oil (79 mg; 0.48 mmol; 96%). NMR spectroscopy consistent with literature.<sup>58</sup> <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 7.00 (d, *J* = 8.5 Hz, 3H), 6.76 (d, *J* = 8.5 Hz, 2H), 2.81 (t, *J* = 7.0 Hz, 2H), 2.73 (t, *J* = 7.0 Hz, 2H), 2.13 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 210.1, 154.3, 132.3, 129.3, 115.5, 45.5, 30.1, 29.0.

**4-(4'-Hydroxyphenyl)butan-2-one (Rheosmin) (5a, Large Scale).** 1,4-Dihydro-2,6-dimethyl-3,5-bis[(methylamino)carbonyl]pyridine (2) (3.01 g; 12.7 mmol), 4-(4'-hydroxyphenyl)-3-buten-2-one (3,4-dehydorrheosmin) (1.38 g; 8.52 mmol), and benzylammonium trifluoroacetate (0.47 g; 2.1 mmol) were placed in a 300 mL reaction tube. To this was added a magnetic stir bar and 125 mL dry THF. The tube was sealed and heated at 70 °C for 16 h. The mixture was cooled to room temperature and 160 mL CH<sub>2</sub>Cl<sub>2</sub> was added. This was washed with 3 M HCl (aq) (3 × 100 mL). All aqueous phases were pooled and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 25 mL). All CH<sub>2</sub>Cl<sub>2</sub> was pooled and dried over Na<sub>2</sub>SO<sub>4</sub>. The liquid was decanted off the Na<sub>2</sub>SO<sub>4</sub>, and the drying agent was rinsed with CH<sub>2</sub>Cl<sub>2</sub> (2 × 10 mL). All CH<sub>2</sub>Cl<sub>2</sub> was pooled, and the solvent removed by rotary evaporation to give a straw colored oil (1.2 g; 7.2 mmol; 84%).

**4-(4'-Hydroxy-3'-methoxyphenyl)butan-2-one (zingerone) (5b).** Following the [general procedure](#) using 4-(4'-hydroxy-3'-methoxyphenyl)but-3-en-2-one (96 mg; 0.50 mmol) provided a pale yellow oil (90 mg; 46 mmol; 93%). NMR spectroscopy consistent with literature.<sup>58</sup> <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 8.2 (d, *J* = 8.0 Hz, 1H), 6.70 (d, *J* = 2.0 Hz, 1H), 6.66 (dd, *J* = 8.0, 2.0 Hz, 1H), 5.60 (s, 1H), 3.86 (s, 3H), 2.82 (t, *J* = 7.4 Hz, 2H), 2.73 (t, *J* = 7.4 Hz, 2H), 2.13 (s, 1H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 208.2, 146.4, 143.9, 132.9, 120.7, 114.4, 111.1, 55.9, 45.5, 30.1, 29.5.

**4-(4'-Hydroxy-3'-methoxyphenyl)butan-2-one (Zingerone) (5b, Large Scale).** Following the [large scale procedure](#) above using 4-(4'-hydroxy-3'-methoxyphenyl)but-3-en-2-one (1.73 g; 9.01 mmol), 1,4-dihydro-2,6-dimethyl-3,5-bis[(methylamino)carbonyl]pyridine (2) (3.01 g; 13.5 mmol), and benzylammonium trifluoroacetate (0.41 g; 1.9 mmol) provided an amber oil. This was dissolved in 10 mL CH<sub>2</sub>Cl<sub>2</sub>/hexane (1:1) and filtered through a 1 cm plug of silica in a 5 cm Buchner funnel. The silica was rinsed further with 200 mL CH<sub>2</sub>Cl<sub>2</sub>/hexane (1:1). All of the filtrate was pooled and evaporated to a straw colored oil (1.55 g; 7.99 mmol; 88.7%).

**4-(4'-*N,N*-Dimethylaminophenyl)butan-2-one (5c).** 1,4-Dihydro-2,6-dimethyl-3,5-bis[(methylamino)carbonyl]pyridine (2) (170 mg; 0.75 mmol), 4-(4'-*N,N*-dimethylaminophenyl)-3-buten-2-one (95 mg; 0.50 mmol), and benzylammonium trifluoroacetate (22 mg; 0.10 mmol) were placed in a 15 mL reaction tube. To this was added a magnetic stir bar and 10 mL dry THF. The tube was sealed and heated at 70 °C for 16 h. The mixture was cooled to room temperature, and solvent was removed by rotary evaporation to give an orange oil. This was dissolved in 40 mL CH<sub>2</sub>Cl<sub>2</sub>/hexane (1:1) and filtered through a 1.5 cm plug of silica. The silica plug was rinsed with 15 mL CH<sub>2</sub>Cl<sub>2</sub>/hexane (1:2). All solvent was pooled and evaporated to a pale yellow oil (80 mg; 0.42 mmol; 84%). NMR spectroscopy consistent with literature.<sup>59</sup> <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 7.06 (d, *J* = 8.7 Hz, 2H), 6.69 (d, *J* = 8.7 Hz, 2H), 2.91 (s, 6H), 2.80 (t, *J* = 7.3 Hz, 2H), 2.71 (t, *J* = 7.3 Hz, 2H), 2.13 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 208.5, 149.2, 128.9, 113.0, 45.6, 40.9, 30.1, 28.9.

**4-Phenylbutan-2-one (5d).** Following the [general procedure](#) using 4-phenyl-3-buten-2-one (73 mg; 50 mmol) provided a pale yellow oil (63 mg; 43 mmol; 86%). NMR spectroscopy consistent with literature.<sup>60</sup> <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 7.27 (t, 2H), 7.18 (m, 3H), 2.89 (t, *J* = 7.6 Hz, 2H), 2.75 (t, *J* = 7.6 Hz, 2H), 2.13 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 207.8, 141.0, 128.5, 128.3, 126.1, 45.2, 30.0, 29.8.

**4-(4'-Bromophenyl)butan-2-one (5e).** Following the [general procedure](#) using 4-(4'-bromophenyl)-3-buten-2-one (110 mg; 50 mmol) provided a nearly colorless oil (110 mg; 49 mmol; 97%). NMR spectroscopy consistent with literature.<sup>61</sup> <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 7.38 (d, *J* = 8.2 Hz, 2H), 7.05 (d, *J* = 8.2 Hz, 2H), 2.84 (t, *J* = 7.4 Hz, 2H), 2.73 (t, *J* = 7.4 Hz, 2H), 2.13 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 207.4, 140.0, 131.5, 130.1, 119.8, 44.8, 30.1, 29.0.

**4-(2',4'-Dichlorophenyl)butan-2-one (5f).** Following the [general procedure](#) using 4-(2',4'-dichlorophenyl)-3-buten-2-one (110 mg; 50 mmol) provided an amber oil (110 mg; 50 mmol; 100%). NMR spectroscopy consistent with literature.<sup>61</sup> <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 7.34 (d, *J* = 2.0 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.15 (dd, *J* = 8.2, 2.0 Hz, 1H), 2.96 (t, *J* = 7.5 Hz, 2H), 2.75 (t, *J* = 7.5 Hz, 2H), 2.15 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 207.1, 137.2, 134.4, 132.6, 131.5, 129.2, 127.1, 42.9, 29.9, 27.1.

**4-(4'-Nitrophenyl)butan-2-one (5g).** Following the [general procedure](#) using 4-(4'-nitrophenyl)-3-buten-2-one (96 mg; 50 mmol) provided a light red oil (70 mg; 36 mmol; 73%). NMR spectroscopy consistent with literature.<sup>61</sup> <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 8.13 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 3.00 (t, *J* = 7.4 Hz, 2H), 2.82 (t, *J* = 7.4 Hz, 2H), 2.16 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 206.5, 148.9, 146.5, 129.2, 123.7, 44.1, 30.0, 29.3.

**4-(1'-Naphthyl)butan-2-one (5h).** Following the [general procedure](#) using 4-(1'-naphthyl)-3-buten-2-one (98 mg; 50 mmol) provided an amber oil (85 mg; 43 mmol; 87%). NMR spectroscopy consistent with literature.<sup>60</sup> <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 7.97 (d, *J* = 8.3 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.48 (m, 2H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 6.9 Hz, 1H), 3.34 (t, *J* = 7.8 Hz, 2H), 2.85 (t, *J* = 7.8 Hz, 2H), 2.13 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 207.9, 137.0, 133.9, 131.6, 128.9, 127.0, 126.03, 125.97, 125.59, 125.58, 123.4, 44.4, 30.1, 26.7.

**2-Decanone (5i).** Following the [general procedure](#) using 3-decen-2-one (77 mg; 0.50 mmol) provided a colorless oil (65 mg; 0.42 mmol; 85% yield + recovery). NMR spectroscopy consistent with literature<sup>62</sup> as a 20/80 mixture of 2-decenone and 2-decanone. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 2.41 (t, *J* = 7.5 Hz, 2H), 2.13 (s, 3H), 1.57 (quintet, *J* = 7.3 Hz, 2H), 1.28 (m, 10H), 0.88 (t, *J* = 6.5 Hz, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ = 209.3, 43.8, 31.8, 29.8, 29.33, 29.17, 29.10, 23.9, 22.6, 14.0.

**4-(4'-Acetamidophenyl)butan-2-one (5j).** 1,4-Dihydro-2,6-dimethyl-3,5-bis[(methylamino)carbonyl]pyridine (2) (168 mg; 0.757 mmol), 4-(4'-acetamidophenyl)-3-buten-2-one (100 mg; 0.50 mmol), and benzylammonium trifluoroacetate (22 mg; 0.10 mmol) were placed in a 15 mL reaction tube. To this was added a magnetic stir bar and 10 mL dry THF. The tube was sealed and heated at 70 °C for 16 h. The mixture was cooled to room temperature, and 25 mL CH<sub>2</sub>Cl<sub>2</sub> was added. This was washed with 3 M HCl (aq) (3 × 25 mL). All aqueous phases were pooled and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 10 mL). All CH<sub>2</sub>Cl<sub>2</sub> was pooled and dried over Na<sub>2</sub>SO<sub>4</sub>. The liquid was decanted off the Na<sub>2</sub>SO<sub>4</sub>, and the

drying agent was rinsed with  $\text{CH}_2\text{Cl}_2$  ( $2 \times 10$  mL). All  $\text{CH}_2\text{Cl}_2$  was pooled, and the solvent removed by rotary evaporation to give an off-white solid (0.10 g; 100%, mp = 113–116 °C). NMR spectroscopy consistent with literature.<sup>63</sup>  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  = 8.23 (s, 1H), 7.41 (d,  $J$  = 8.4 Hz, 1H), 7.09 (d,  $J$  = 8.4 Hz, 1H), 2.84 (t,  $J$  = 7.5 Hz, 1H), 2.73 (t,  $J$  = 7.5 Hz, 1H), 2.130 (s, 1H), 2.126 (s, 1H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  = 208.2, 168.8, 136.7, 136.1, 128.5, 120.2, 45.0, 30.0, 29.0, 24.2.

## ■ ASSOCIATED CONTENT

### 📄 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00041.

$^1\text{H}$  NMR and  $^{13}\text{C}$  NMR for all transformations. Calculated  $\text{pK}_a$  and  $\log D$  values for Hantzsch pyridines and dihydropyridines (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We are grateful to Lisa Mertzman for procurement of materials, Beth Buckwalter for NMR spectroscopy, Ed Fenlon and Laszlo Kürti for helpful discussions, and Franklin and Marshall College for funding.

## ■ REFERENCES

- Ito, J.; Nishiyama, H. *Tetrahedron Lett.* **2014**, *55*, 3133.
- Brieger, G.; Nestrick, T. J. *Chem. Rev.* **1974**, *74*, 567.
- Johnstone, R. A. W.; Wilby, A. H.; Entwistle, I. D. *Chem. Rev.* **1985**, *85*, 129.
- Wang, C.; Wu, X.; Xiao, J. *Chem. - Asian J.* **2008**, *3*, 1750.
- Wang, D.; Astruc, D. *Chem. Rev.* **2015**, *115*, 6621.
- Zhu, C.; Saito, K.; Yamanaka, M.; Akiyama, T. *Acc. Chem. Res.* **2015**, *48*, 388.
- Chikashita, H.; Miyazaki, M.; Itoh, K. *Synthesis* **1984**, *1984*, 308.
- Saito, K.; Miyashita, H.; Akiyama, T. *Org. Lett.* **2014**, *16*, 5312.
- Zhu, C.; Falck, J. R. *ChemCatChem* **2011**, *3*, 1850.
- Saito, K.; Horiguchi, K.; Shibata, Y.; Yamanaka, M.; Akiyama, T. *Chem. - Eur. J.* **2014**, *20*, 7616.
- Chen, Q.-A.; Gao, K.; Duan, Y.; Ye, Z.-S.; Shi, L.; Yang, Y.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2012**, *134*, 2442.
- Chen, Z. P.; Chen, M. W.; Guo, R. N.; Zhou, Y. G. *Org. Lett.* **2014**, *16*, 1406.
- Zhu, X. Q.; Zhang, M. T.; Yu, A.; Wang, C. H.; Cheng, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 2501.
- Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223.
- Voet, D.; Voet, J. G. *Biochemistry*; 4th ed.; John Wiley & Sons: Hoboken, NJ, 2011.
- Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1.
- Norcross, B. E.; Klinedinst, P. E.; Westheimer, F. H. *J. Am. Chem. Soc.* **1962**, *84*, 797.
- Gase, R. A.; Pandit, U. K. *J. Am. Chem. Soc.* **1979**, *101*, 7059.
- Nakamura, K.; Fujii, M.; Ohno, A.; Oka, S. *Tetrahedron Lett.* **1984**, *25*, 3983.
- Torchy, S.; Cordonnier, G.; Barbry, D.; Vanden, E. J. *J. Molecules* **2002**, *7*, 528.
- Garden, S. J.; Guimaraes, C. R. W.; Correa, M. B.; de Oliveira, C. A. F.; Pinto, A. D.; de Alencastro, R. B. *J. Org. Chem.* **2003**, *68*, 8815.
- Yang, J. W.; Hechavarria Fonseca, M. T.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 6660.
- Saini, A.; Kumar, S.; Sandhu, J. S. *J. Sci. Ind. Res.* **2008**, *67*, 95.
- Kuthan, J.; Kurfurst, A. *Ind. Eng. Chem. Prod. Res. Dev.* **1982**, *21*, 191.
- Mayer, S.; List, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4193.
- Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32.
- Adolfsson, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 3340.
- You, S.-L. *Chem. - Asian J.* **2007**, *2*, 820.
- Connon, S. J. *Org. Biomol. Chem.* **2007**, *5*, 3407.
- Ouellet, S. G.; Walji, A. M.; Macmillan, D. W. C. *Acc. Chem. Res.* **2007**, *40*, 1327.
- Rueping, M.; Sugiono, E.; Schoepke, F. R. *Synlett* **2010**, *2010*, 852.
- Rueping, M.; Dufour, J.; Schoepke, F. R. *Green Chem.* **2011**, *13*, 1084.
- Marcelli, T. *Asymmetric Transfer Hydrogenations Using Hantzsch Esters*; Springer-Verlag: Berlin, 2011.
- Zheng, C.; You, S.-L. *Chem. Soc. Rev.* **2012**, *41*, 2498.
- Bhalla, V.; Tejpal, R.; Kumar, M. *Dalton Transactions* **2012**, *41*, 403.
- de Vries, J. G.; Mrcic, N. *Catal. Sci. Technol.* **2011**, *1*, 727.
- Modified bezothiazolones have been demonstrated to be readily removable hydrogen sources for transfer hydrogenation; see ref 5.
- Richter, D.; Mayr, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 1958.
- Shi, J.; Huang, X. Y.; Wang, H. J.; Fu, Y. *J. Chem. Inf. Model.* **2012**, *52*, 63.
- Zhu, X.-Q.; Tan, Y.; Cao, C.-T. *J. Phys. Chem. B* **2010**, *114*, 2058.
- Horn, M.; Schappele, L. H.; Lang-Wittkowski, G.; Mayr, H.; Ofial, A. R. *Chem. - Eur. J.* **2013**, *19*, 249.
- Personal communication with X.-Q. Zhu
- Gelbard, G.; Lin, J.; Roques, N. J. *Org. Chem.* **1992**, *57*, 1789.
- Nomura, M.; Nakata, S.; Hamada, F. *Nippon Kagaku Kaishi* **2002**, 141.
- Tuttle, J. B.; Ouellet, S. p. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 12662.
- Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368.
- Zumbansen, K.; Doehring, A.; List, B. *Adv. Synth. Catal.* **2010**, *352*, 1135.
- Percent yield + recovery is presented as the mass percent of isolated ketone product and enone starting material relative to the starting mass of the enone.
- See the Supporting Information for additional NMR spectra.
- Morimoto, C.; Satoh, Y.; Hara, M.; Inoue, S.; Tsujita, T.; Okuda, H. *Life Sci.* **2005**, *77*, 194.
- Bhutani, K. K.; Birari, R.; Kapat, K. *Nat. Prod. Commun.* **2007**, *2*, 331.
- Yun, J. W. *Phytochemistry* **2010**, *71*, 1625.
- Lopez, H. L.; Ziegenfuss, T. N.; Hofheins, J. E.; Habowski, S. M.; Arent, S. M.; Weir, J. P.; Ferrando, A. A. *J. Int. Soc. Sports Nutr.* **2013**, *10*, 22.
- Park, K. S. *Pharm. Biol.* **2015**, *53*, 870.
- Calculator Plugins were used for structure property prediction and calculation: Marvin 16.2.29.0, ChemAxon: Budapest, Hungary, 2016; <http://www.chemaxon.com>, accessed March 2, 2016 (see Supporting Information).
- See Supporting Information.
- Smith, L. *Chem. Educ.* **1996**, *1*, 1.
- Dickson, D. P.; Toh, C.; Lunda, M.; Yermolina, M. V.; Wardrop, D. J.; Landrie, C. L. *J. Org. Chem.* **2009**, *74*, 9535.
- Lauer, M. G.; Thompson, M. K.; Shaughnessy, K. H. *J. Org. Chem.* **2014**, *79*, 10837.
- Li, X.; Li, L.; Tang, Y.; Zhong, L.; Cun, L.; Zhu, J.; Liao, J.; Deng, J. *J. Org. Chem.* **2010**, *75*, 2981.
- Cao, J.-J.; Zhou, F.; Zhou, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4976.
- Keaton, K. A.; Phillips, A. J. *Org. Lett.* **2007**, *9*, 2717.
- Romesberg, F. E.; Flanagan, M. E.; Uno, T.; Schultz, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 5160.