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Pages: 9

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### Asymmetric Catalysis

The combination of a chiral amine catalyst and a copper complex allows the synthesis of  $\alpha,\beta$ -disubstituted aldehydes from unsaturated aldehydes with good yields and excellent stereoselectivity.



R' = CH<sub>2</sub>NO<sub>2</sub> or CH(CO<sub>2</sub>Et)<sub>2</sub> Yield = 44–99% R'' =  $\frac{2}{2}$  0 78-95% de R'' =  $\frac{2}{2}$  0 94-99% ee

JH. Kim, E.	J. Park, HJ. Lee,	
ХН. Но, Н.	-S. Yoon, P. Kim, H. Yun	,
HY. Jang*	••••••	1–9

Tandem Iminium/Copper Catalysis: Highly Enantioselective Synthesis of  $\alpha,\beta$ -Disubstituted Aldehydes

Keywords: Synthetic methods / Asymmetric catalysis / Copper / Michael addition / Aldehydes



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Date: 25-05-13 11:17:51

Pages: 9

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# Tandem Iminium/Copper Catalysis: Highly Enantioselective Synthesis of α,β-Disubstituted Aldehydes

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Keywords: Synthetic methods / Asymmetric catalysis / Copper / Michael addition / Aldehydes

With the goal of synthesizing biologically and synthetically valuable products under environmentally benign and economic conditions, an asymmetric organocatalytic reaction was combined with a copper catalytic reaction. This iminium/copper catalysis allowed highly optically active  $\alpha$ , $\beta$ -disubstituted aldehydes to be synthesized with good yields in one-pot fashion. The  $\beta$ -substitution took place through iminium-cata-

### Introduction

Multicatalytic reactions involving transition-metal complexes and organocatalysts have emerged as powerful tools for highly stereoselective step-economic multibond formation.<sup>[1,2]</sup> With the aim of developing highly stereoselective multiple-bond-forming catalytic reactions for synthesizing pharmaceutically and synthetically valuable compounds, we recently reported asymmetric syntheses of  $\alpha$ , $\beta$ -disubstituted aldehydes by means either of tandem iminium/ruthenium(II)-catalyzed photoreactions<sup>[3]</sup> or of iminium/coppercatalyzed reactions.<sup>[4]</sup> Although catalytic reaction conditions for forming each single bond were reported, optimization for a multistep one-pot process is still challenging.<sup>[5–7]</sup> Judicious choices of organocatalysts, additives, and solvents are prerequisite for high yields and stereoselectivities of the tandem multicatalytic reactions.

In the context of expanding the scope of  $\alpha$ , $\beta$ -substitution of aldehydes under multicatalytic conditions, installation of a nitroalkyl substituent at the  $\beta$ -position of the aldehyde by asymmetric iminium catalysis together with addition of TEMPO (2,2,6,6-tetramethylpiperidin-1-yloxyl) at the  $\alpha$ position through a copper-catalyzed reaction was considered. Michael addition of nitromethane to  $\alpha$ , $\beta$ -unsaturated aldehydes by enantioselective iminium catalysis<sup>[5,6,8,9]</sup> and  $\alpha$ -oxyamination of saturated aldehydes through photoreaclyzed Michael addition of nitromethane or diethyl malonate to the  $\alpha,\beta$ -unsaturated aldehydes, followed by copper-assisted addition of TEMPO (2,2,6,6-tetramethylpiperidin-1-yloxyl) at the aldehyde  $\alpha$ -position. An iminium/copper-catalyzed tandem addition product was converted into a 3,4,5-trisubstituted piperidine for X-ray crystallographic analysis.

tions<sup>[10]</sup> or metal-catalyzed reactions<sup>[11]</sup> have both been reported, but the combination of these reactions in a onepot process has not been reported so far. Optically active nitroaldehydes have potential for use in the syntheses of biologically important  $\gamma$ -aminocarbonyl, aminoalkane, and 2-pyrrolidone derivatives.<sup>[12,13]</sup> Abundant examples of asymmetric organocatalytic reactions for highly stereoselective substitution of nitroaldehydes have consequently been reported.<sup>[9,14]</sup> Iminium-catalyzed nitroalkane addition to  $\alpha$ ,  $\beta$ -unsaturated aldehydes affords  $\beta$ -substituted nitroaldehydes, whereas enamine-catalyzed aldehyde addition to nitroolefins gives  $\alpha$ ,  $\beta$ -disubstituted nitroaldehydes, both with high stereoselectivities. In terms of diversity-oriented synthesis, investigation into catalytic reactions for installation of various functional groups at different positions in aldehydes might contribute to the building of libraries of optically active nitroaldehyde collections for further application in the pharmaceutical and fine chemical industries. Although enamine-catalyzed aldehyde addition to nitroolefins sets two stereogenic centers with high enantio- and diastereoselectivities, the functional groups introduced onto the aldehydes in such cases are alkyl or aromatic groups. In this study, through the employment of iminium catalysis and copper-catalyzed TEMPO addition, syntheses of  $\alpha$ -oxyaminated,  $\beta$ -aryl- or  $\beta$ -alkyl-substituted nitroaldehydes with excellent enantio- and diastereoselectivities have been demonstrated.

To allow further investigation of multiple-catalytic tandem additions of nucleophiles and TEMPO to  $\alpha$ , $\beta$ -unsaturated aldehydes, previously reported multiple-catalytic tandem additions of diethyl malonate and TEMPO to  $\alpha$ , $\beta$ -unsaturated aldehydes under copper-catalyzed conditions were revisited.<sup>[4]</sup> Iminium/copper-based multiple-bond-forming

2

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Date: 25-05-13 11:17:51

Pages: 9

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Iminium/Cu Catalysis

catalysis affords a wide range of  $\alpha$ , $\beta$ -disubstituted aldehydes in one-pot fashion with good yields and high enantioselectivities. Depending on the nucleophiles, different reaction conditions are required, as discussed in this report.

### **Results and Discussion**

To implement tandem nitromethane/TEMPO addition to aldehydes, (*S*)-2-[diphenyl(trimethylsilyloxy)methyl]pyrrolidine (**A**, Table 1) and metal complexes (copper and iron complexes) were used. Chiral pyrrolidine **A** forms a chiral iminium intermediate for nitromethane addition, and the resulting enamine intermediates produced by nitromethane addition to the iminium system react with an ionic electrophilic metal-TEMPO complex.<sup>[11,15]</sup> The role of each catalyst is considered in the context of previously reported tandem oxidation/malonate addition/oxyamination sequences with allylic alcohols in the presence of copper complexes and chiral organocatalysts.<sup>[4]</sup> To optimize the stereoselective tandem  $\alpha$ , $\beta$ -functionalization of aldehydes, different solvents, copper species, additives, and organocatalysts were tested.

Table 1. Optimization of tandem nitromethane/TEMPO addition to **1a**.

Metal catalyst (10 mol-%)NO₂ OCatalyst A (20 mol%) ፤							
H Ph CH <sub>3</sub> NO <sub>2</sub> (3 equiv.) H Ph Additive (10 mol <sup>-</sup> %), TEMPO (2 equiv.) H O <sub>2</sub> (bubbling), r.t. Solvent (0.4 M)							
Entry	Metal catalyst	Solvent	Additive	Yield	de <sup>b</sup>		
1	CuCl	DMF	PhCO <sub>2</sub> H	43 % <sup>a</sup>	>95 %		
2	CuCl	CH <sub>3</sub> CN	PhCO <sub>2</sub> H	32 % <sup>a</sup>	>95 %		
3	CuCl	CH <sub>2</sub> Cl <sub>2</sub>	PhCO <sub>2</sub> H	40 % <sup>a</sup>	>95 %		
4	CuCl	CHCl <sub>3</sub>	PhCO <sub>2</sub> H 60	% <sup>a</sup> (63 %)	>95 %		
5	CuCl	Toluene	PhCO <sub>2</sub> H	44 %	>95 %		
6	CuBr <sub>2</sub>	CHCl <sub>3</sub>	PhCO <sub>2</sub> H	25 % <sup>a</sup>	>95 %		
7	Cu(OTf) <sub>2</sub>	CHCl <sub>3</sub>	PhCO <sub>2</sub> H	34 % <sup>a</sup>	>95 %		
8	Cu <sub>2</sub> O	CHCl <sub>3</sub>	PhCO <sub>2</sub> H				
9	CuO	CHCl <sub>3</sub>	PhCO <sub>2</sub> H				
10	[Fe(phen)3][PF6)3	CHCl <sub>3</sub>	PhCO <sub>2</sub> H				
11	CuCl	CHCl <sub>3</sub>	AdamCO <sub>2</sub> H	65 %	>95 %		
12	CuCl	CHCI <sub>3</sub>	LiOAc	45%	>95 %		

 $^{\rm a}$  0.5 M concentration,  $^{\rm b}$  Compound  ${\rm 1b}$  was observed as a single diastereomerby  $^{\rm 1}{\rm H}$  NMR.



AdamCO<sub>2</sub>H = Adamantane-1-carboxylic acid

A solution of cinnamaldehyde (1a, Table 1), nitromethane (3 equiv.), and TEMPO (2 equiv.) was treated with CuCl (10 mol-%) and catalyst A (20 mol-%) under aerobic conditions in the solvent indicated (Entries 1–5). Benzoic acid (10 mol-%) was added to accelerate the iminium salt formation.<sup>[5-7]</sup> The highest yield of **1b** was obtained with CHCl<sub>3</sub> (Entry 4). In DMF, CH<sub>3</sub>CN, and CH<sub>2</sub>Cl<sub>2</sub> the addition of nitromethane to 1a was not efficient, showing lower yields. CuBr2 and Cu(OTf)2 as copper sources provided product 1b in diminished yields (Entries 6 and 7). Copper oxide (Cu<sub>2</sub>O and CuO) did not promote this transformation (Entries 8 and 9). In addition to copper complexes, an iron(III) complex that promoted the addition of TEMPO to enamine species was used,<sup>[11]</sup> but formation of 1b was not observed (Entry 10). For promotion of nitromethane addition, adamantanecarboxylic acid and LiOAc base additives were also tested (in addition to benzoic acid), and afforded 1b in 65% (adamantanecarboxylic acid) and 45% (LiOAc) yields (Entries 11 and 12). Compound 1b was observed as a single diastereomer by <sup>1</sup>H NMR (>95% de). The relative stereochemistry was assigned on the basis of previous organocatalyzed nitromethane additions to  $\alpha,\beta$ unsaturated aldehydes and TEMPO additions to hydrocinnamaldehyde.[3,4,9-11]

In view of the results of the solvent and metal screening of tandem nitromethane/TEMPO addition, previously reported enantioselective tandem allylic alcohol oxidations and malonate/TEMPO additions to aldehydes in the presence of CuCl and catalyst A were re-examined. In the previously developed three-step, one-pot reactions, the use of DMF as a solvent and a CuCl·TEMPO complex was required for complete oxidation of the allylic alcohols, to generate  $\alpha,\beta$ -unsaturated aldehydes. The employment of an  $\alpha$ , $\beta$ -unsaturated aldehyde as the starting material allowed the in situ oxidation of an allylic alcohol to be omitted. A wide range of metal species (mostly copper complexes) and solvents were therefore applied to tandem additions of diethyl malonate and TEMPO to  $\alpha,\beta$ -unsaturated aldehyde 1a (Table 2). A variety of different solvents (DMF, CH<sub>3</sub>CN, CH2Cl2, CHCl3, and toluene) were tested; the best yield (80%) was obtained with CH<sub>3</sub>CN (Entries 1–5).

Copper and iron complexes were then tested.  $CuBr_2$ ,  $Cu-(OTf)_2$ , and CuCl showed good catalytic activities for this transformation (Entries 6–10). As well as adamantane-carboxylic acid, benzoic acid and LiOAc were also used, providing **1c** in 55% and 50% yields, respectively (Entries 11 and 12).

The reactivities of chiral organocatalysts were next compared (Table 3). For nitromethane/TEMPO addition, CuCl in CHCl<sub>3</sub> was used (Table 1, Entry 4). The pyrrolidine-type catalysts **A** and **B** catalyzed the reaction to afford the desired tandem product 1**b**, whereas the imidazolidinone-type catalysts **C** and **D** did not. Similarly, for the formation of 1**c**, catalysts **A** and **B** showed good activities, but catalysts **C** and **D** provided only malonate addition products. The optimized conditions from Table 2 were used to form 1**c**. The substituent on catalyst **B** is smaller than that on **A**, and this reduces the enantiopurities of 1**b** and 1**c**.

Next, a range of  $\alpha$ , $\beta$ -unsaturated aldehydes were subjected to tandem Michael/TEMPO addition. As listed in Table 4, nitromethane and diethyl malonate were used as the nucleophiles for the Michael addition. Tandem nitromethane/TEMPO addition to  $\alpha$ , $\beta$ -unsaturated aldehydes

Pages: 9

# FULL PAPER

Table 2. Optimization of tandem malonate/TEMPO addition to 1a.

0	Metal catalyst (10 mol-%) Catalyst <b>A</b> (20 mol-%)	EtO <sub>2</sub> C CO <sub>2</sub> Et
H Ph	$CH_2(CO_2Et)_2$ (3 equiv.)	H Ph R
1a Additi	ve (10 mol <sup>-</sup> %), TEMPO (2 eq O <sub>2</sub> (bubbling), r.t.	<sup>uiv.)</sup> 1c
	Solvent (0.4 M)	

Entry	Metal catalyst	Solvent	Additive (10 mol-%)	Yield	de <sup>a</sup>
1	CuCl	DMF	AdamCO <sub>2</sub> H	36 %	>95 %
2	CuCl	CH <sub>3</sub> CN	AdamCO <sub>2</sub> H	80 %	>95 %
3	CuCl	$CH_2CI_2$	AdamCO <sub>2</sub> H	66 %	>95 %
4	CuCl	CHCI <sub>3</sub>	AdamCO <sub>2</sub> H	44 %	>95 %
5	CuCl	Toluene	AdamCO <sub>2</sub> H	57 %	>95 %
6	CuBr <sub>2</sub>	CH <sub>3</sub> CN	AdamCO <sub>2</sub> H	70 %	>95 %
7	Cu(OTf) <sub>2</sub>	CH <sub>3</sub> CN	AdamCO <sub>2</sub> H	80 %	>95 %
8	Cu <sub>2</sub> O	CH <sub>3</sub> CN	AdamCO <sub>2</sub> H		>95 %
9	CuO	CH <sub>3</sub> CN	AdamCO <sub>2</sub> H		>95 %
10 [	Fe(phen) <sub>3</sub> ][PF <sub>6</sub> ) <sub>3</sub>	CH <sub>3</sub> CN	AdamCO <sub>2</sub> H		>95 %
11	CuCl	CH <sub>3</sub> CN	PhCO <sub>2</sub> H	55 %	>95 %
12	CuCl	CH <sub>3</sub> CN	LiOAc	50 %	>95 %

<sup>a</sup> Compound **1c** was observed as a single diastereomer by <sup>1</sup>H NMR.



AdamCO<sub>2</sub>H = Adamantane-1-carboxylic acid

Table 3. Optimization of organocatalysts.



mainly favored the conditions involving CuCl, organocatalyst **A**, and benzoic acid as additive in CHCl<sub>3</sub>. Cinnamaldehyde (**1a**) and its phenyl-substituted derivatives **2a** and **3a** were transformed into  $\alpha$ , $\beta$ -substituted nitroaldehydes **1b**, **2b**, and **3b** in good yields and with excellent stereoselectivities. The  $\alpha$ , $\beta$ -unsaturated aldehydes containing naphthalene (compound **4a**), nitro-substituted phenyl (compound **5a**), and thiophene groups (compound **6a**) showed slightly lower yields but high stereoselectivities. The cyclopropyl-substituted aldehyde 7a also participated in this reaction, affording 7b in 64% yield but with slightly decreased diastereo-(78% *de*) and enantioselectivity (94% *ee*).

Table 4. Substrate scope.



<sup>a</sup> Method A: CuCl (10 mol-%), catalyst A (20 mol-%), PhCO<sub>2</sub>H (10 mol-%) in CHCl<sub>3</sub> <sup>b</sup> Method B: Cu(OTf)<sub>2</sub> (10 mol-%), catalyst A (20 mol-%), adamantane carboxylic acid (10 mol-%) in CH<sub>3</sub>CN

 $^{\rm c}$  CuCl (10 mol-%), catalyst A (20 mol-%), adamantane carboxylic acid (10 mol-%) in CH\_3CN



4

Date: 25-05-13 11:17:51

Pages: 9

#### Iminium/Cu Catalysis

In the case of tandem malonate/TEMPO addition, a mixture of Cu(OTf)<sub>2</sub> (or CuCl), catalyst **A**, and the adamantanecarboxylic acid additive in CH<sub>3</sub>CN was employed. As in the addition of nitromethane, cinnamaldehyde (**1a**) and its phenyl-substituted derivatives **2a** and **3a** participated in tandem malonate/TEMPO addition to afford **1c**–**3c** with good yields and excellent stereoselectivities. The naphthyl-substituted aldehyde **4c** showed slightly reduced yields (57%) but high diastereo- and enantioselectivities. The nitro-substituted cinnamaldehyde **5c** and thiophene-substituted aldehyde **6c** gave the highest yields and good stereo-selectivities. The cyclopropyl-substituted compound **7c** was tested with both CuCl and Cu(OTf)<sub>2</sub>; a higher yield and selectivity (44% yield and 96% *ee*) were obtained with CuCl than with Cu(OTf)<sub>2</sub> (40% yield and 93% *ee*).

The tandem addition products can be converted into heterocyclic compounds with potential pharmaceutical and biological activities.<sup>[16]</sup> As an example, the bromo-substituted compound **8c** was synthesized under the copper/organocatalytic conditions, with subsequent reductive amination/cyclization providing 3,4,5-trisubstituted piperidine derivative **8d** in 66% yield (Scheme 1). A single crystal of



Figure 1. The molecular structure of 8d.

compound **8d** suitable for X-ray crystallography (Figure 1) was obtained from a solvent mixture of dichloromethane and hexane (evaporation at -20 °C). The X-ray crystallo-



Scheme 1. Synthesis of 3,4,5-trisubstituted piperidine 8d from 8a.



Scheme 2. Proposed catalytic cycle.

Pages: 9

# FULL PAPER

graphic data for **8d** also confirmed the relative and absolute stereochemistry of **8c**.

A proposed catalytic cycle for tandem nucleophilic nitromethane and malonate/TEMPO addition is given in Scheme 2. It begins with formation of iminium salt I from cinnamaldehyde and an organocatalyst. The subsequent addition of a nucleophile to the  $\beta$ -position of iminium I provides enamine intermediate II, which undergoes either hydrolysis or copper-TEMPO addition. In the presence of TEMPO and the copper complex, intermediate II reacts with the copper-TEMPO complex to afford an  $\alpha,\beta$ -disubstituted aldehyde. The structure and reactivity of the copper-TEMPO complex was proposed in investigations of CuCl<sub>2</sub>/ TEMPO-catalyzed alcohol oxidations and CuCl<sub>2</sub>-catalyzed  $\alpha$ -oxyamination of aldehydes.<sup>[11c,17]</sup> Copper(I) complexes that were either added at the beginning of the reaction or generated during the reaction underwent oxidation in the presence of TEMPO or oxygen, forming active copper(II)-TEMPO complexes.

### Conclusions

A tandem protocol based on iminium and copper catalysis produced highly optically active  $\alpha$ , $\beta$ -disubstituted aldehydes. A wide range of  $\alpha$ -oxyaminated and  $\beta$ -alkylated aldehydes were synthesized under the optimized conditions for each  $\beta$ -alkylating agent. Depending on the nucleophile for  $\beta$ -alkylation, different copper sources, solvents, and additives were employed; in terms of chiral amine catalysts, catalyst **A** mainly gave good conversions and stereoselectivities. One of  $\alpha$ , $\beta$ -disubstituted aldehydes was cyclized to provide the 3,4,5-trisubstituted piperidine; this demonstrates potential applications of this method for the synthesis of biologically useful building block. Overall, this tandem transformation might offer environmentally benign and step-economic processes for the syntheses of pharmaceutically, biologically, and synthetically useful aldehydes.

### **Experimental Section**

General Procedure for the Tandem Nitromethane/TEMPO Addition: A mixture of aldehyde (0.5 mmol), CuCl (10 mol-%), TEMPO (S)-2-[diphenyl(trimethylsilyloxy)methyl]pyrrolidine (2 equiv.), (10 mol-%), benzoic acid (10 mol-%), and nitromethane (3 equiv.) in CHCl<sub>3</sub> (0.4 M) was stirred under oxygen (1 atm). The solvent was removed with a rotary evaporator to produce a residue, which was purified by column chromatography on silica gel with elution with hexane and ether. To confirm the enantioselectivity and yield of 1b, the compound was exposed to reduction conditions. Reduction conditions: the aldehyde (1 equiv.) was treated with an anhydrous THF solution containing NaBH<sub>4</sub> (4 equiv.) at 0 °C for 50 min, and the reaction mixture was then stirred for 12 h at room temperature, to afford the alcohol 1d. The diastereopurity of each compound was measured by <sup>1</sup>H NMR and the enantiopurity was measured by HPLC analysis.

**4-Nitro-3-phenyl-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)butanal** (**1b**): The representative experimental procedure was applied to compound **1a** (66 mg, 0.5 mmol) for 4 h to yield product **1b** 

(104 mg, 60%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 1.12–1.55 (m, 18 H), 4.09 (m, 1 H), 4.43 (m, 1 H), 4.74 (m, 1 H), 4.94 (m, 1 H), 7.19 (d, *J* = 8 Hz, 2 H), 7.29 (m, 4 H), 9.75 (d, *J* = 0.8 Hz, 1 H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 Hz):  $\delta$  = 14.4, 17.2, 20.9, 22.9, 31.8, 34.3, 40.1, 40.3, 45.0, 60.3, 61.8, 76.6, 87.5, 128.3, 128.4, 128.7, 129.0, 134.2, 201.2 ppm. IR (neat):  $\tilde{v}$  = 2974, 2932, 1730, 1556, 1455, 1377, 1257, 1047, 700 cm<sup>-1</sup>. HRMS calcd. for C<sub>19</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub> [M + H]<sup>+</sup> 349.2127; found 349.2127. HPLC Chiracel AD-H 99:1 (hexane/*i*PrOH), 210 nm, 0.5 mLmin<sup>-1</sup>, retention time 22.7 min (minor) and 24.5 min (major).

**4-Nitro-3-phenyl-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)butan-1-ol** (1d): The representative experimental procedure for the catalytic reaction and hydrogenation was applied to compound **1a** (67 mg, 0.5 mmol) to yield product **1d** (110 mg, 63%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta = 1.12$ –1.60 (m, 18 H), 3.40 (d, J = 10.8 Hz, 1 H), 3.53 (m, 1 H), 3.98 (t, J = 11.0 Hz, 1 H), 4.54 (t, J = 9.4 Hz, 1 H), 4.63 (m, 1 H), 4.97 (m, 1 H), 5.97 (s, 1 H), 7.18 (d, J = 7.6 Hz, 1 H), 7.30 (m, 1 H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 Hz):  $\delta = 17.3$ , 21.1, 21.1, 32.6, 34.9, 40.1, 40.6, 46.3, 60.5, 62.3, 66.7, 77.7, 82.2, 127.9, 128.2, 129.1, 136.7 ppm. IR (neat):  $\tilde{v} = 2930$ , 1555, 1454, 1379, 1256, 1053, 701 cm<sup>-1</sup>. HRMS calcd. for C<sub>19</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub> [M + H]<sup>+</sup> 351.2284; found 351.2284. HPLC Chiracel OD-H 90:10 (hexane/*i*PrOH), 210 nm, 0.5 mL min<sup>-1</sup>, retention time 20.6 min (minor) and 26.4 min (major).

**4-Nitro-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)-3-***p***-tolylbutanal** (2b): The representative experimental procedure was applied to compound **2a** (73 mg, 0.5 mmol) for 4 h to yield product **2b** (110 mg, 61%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta = 1.12-1.55$  (m, 18 H), 2.30 (s, 1 H), 4.05 (m, 1 H), 4.40 (m, 1 H), 4.70 (m, 1 H), 4.92 (m, 1 H), 7.09 (m, 4 H), 9.71 (d, J = 4.4 Hz, 1 H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 Hz):  $\delta = 17.0$ , 20.6, 20.7, 21.2, 34.1, 34.2, 39.9, 40.2, 44.5, 60.1, 61.6, 87.4, 128.0, 129.6, 130.8, 138.0, 200.8 ppm. IR (neat):  $\tilde{v} = 2974$ , 2930, 1730, 1556, 1465, 1377, 1257, 1241, 733 cm<sup>-1</sup>. HRMS calcd. for C<sub>20</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub> [M + H]<sup>+</sup> 363.2284; found 363.2284. HPLC Chiracel OD-H 99:1 (hexane/*i*PrOH), 254 nm, 0.5 mL min<sup>-1</sup>, retention time 20.8 min (major) and 23.5 min (minor).

**3-(4-Methoxyphenyl)-4-nitro-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)butanal (3b):** The representative experimental procedure was applied to compound **3a** (81 mg, 0.5 mmol) for 3.5 h to yield product **3b** (113 mg, 60%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta = 1.13-1.55$  (m, 18 H), 3.77 (s, 1 H), 4.02 (m, 1 H), 4.39 (m, 1 H), 4.69 (m, 1 H), 4.92 (m, 1 H), 6.83 (d, J = 8.0 Hz, 2 H), 7.10 (d, J = 8.0 Hz, 2 H), 9.71 (d, J = 4.0 Hz, 1 H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 Hz):  $\delta = 17.2$ , 20.7, 20.8, 34.2, 34.3, 40.1, 40.3, 44.3, 55.3, 60.2, 61.7, 76.8, 77.0, 77.2, 77.5, 87.5, 114.4, 125.9, 129.4, 159.4, 201.0 ppm. IR (neat):  $\tilde{v} = 2935$ , 1730, 1515, 1378, 1254, 1035, 736 cm<sup>-1</sup>. HRMS calcd. for C<sub>20</sub>H<sub>30</sub>N<sub>2</sub>O<sub>5</sub> [M + H]<sup>+</sup> 379.2233; found 379.2233. HPLC Chiracel AD-H 95:5 (hexane/*i*PrOH), 254 nm, 0.5 mL min<sup>-1</sup>, retention time 15.7 min (minor) and 18.1 min (major).

**3-(Naphthalen-2-yl)-4-nitro-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)butanal (4b):** The representative experimental procedure was applied to compound **3a** (91 mg, 0.5 mmol) for 3 h to yield product **4b** (88 mg, 44%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 1.12–1.53 (m, 18 H), 4.26 (m, 1 H), 4.53 (m, 1 H), 4.84 (m, 1 H), 5.02 (m, 1 H), 7.31 (d, *J* = 8.4 Hz, 1 H), 7.45 (m, 2 H), 7.65 (s, 1 H), 7.79 (m, 3 H), 9.79 (d, *J* = 4.4 Hz, 1 H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 Hz):  $\delta$ = 17.0, 20.6, 20.7, 34.1, 39.9, 40.2, 45.0, 60.1, 61.6, 74.5, 87.3, 125.3, 126.2, 126.3, 127.4, 127.6, 127.6, 128.6, 128.8, 131.5, 132.8, 133.0, 201.0 ppm. IR (neat):  $\tilde{v}$  = 2974, 2931, 1730, 1555, 1467, 1376, 1241, 1131, 735 cm<sup>-1</sup>. HRMS calcd. for C<sub>23</sub>H<sub>30</sub>N<sub>2</sub>O<sub>4</sub> [M + H]<sup>+</sup> 399.2284; found 399.2284. HPLC Chiracel AD-H 95:5 Iminium/Cu Catalysis

Date: 25-05-13 11:17:51

Pages: 9

Eurjoc European Journal

(hexane/*i*PrOH), 254 nm, 0.5 mLmin<sup>-1</sup>, retention time 21.6 min (major) and 27.4 min(minor).

**4-Nitro-3-(4-nitrophenyl)-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)butanal (5b):** The representative experimental procedure was applied to compound **5a** (88 mg, 0.5 mmol) for 7 h to yield product **5b** (106 mg, 54%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta = 1.10-1.50$  (m, 18 H), 4.23 (d, J = 7.5 Hz, 1 H), 4.49 (s, 1 H), 4.83 (m, 1 H), 4.96 (m, 1 H), 7.44 (d, J = 8.5 Hz, 2 H), 8.21 (d, J = 8.5 Hz, 2 H), 9.91 (d, J = 2.0 Hz, 1 H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 Hz):  $\delta = 16.8$ , 17.0, 20.6, 20.7, 27.5, 29.6, 33.9, 34.1, 39.9, 40.2, 44.4, 60.5, 61.8, 86.7, 124.1, 129.5, 142.3, 147.8, 201.3 ppm. IR (neat):  $\tilde{v} = 2925$ , 2853, 1729, 1524, 1469, 1376, 1374, 1258, 720 cm<sup>-1</sup>. HRMS calcd. for C<sub>19</sub>H<sub>27</sub>N<sub>3</sub>O<sub>6</sub> [M + H]<sup>+</sup> 394.1978; found 394.1978. HPLC Chiracel AS-H 80:20 (hexane/*i*PrOH), 254 nm, 0.5 mLmin<sup>-1</sup>, retention time 26.1 min (minor) and 32.3 min (major).

**4-Nitro-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)-3-(thiophen-2-yl)butanal (6b):** The representative experimental procedure was applied to compound **6a** (69 mg, 0.5 mmol) for 9 h to yield product **6b** (82 mg, 46%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta = 1.11-1.51$  (m, 18 H), 4.43 (m, 2 H), 4.71 (m, 1 H), 4.89 (m, 1 H), 6.89 (d, J =2.8 Hz, 1 H), 6.94 (t, J = 4.4 Hz, 1 H), 7.25 (m, 1 H), 9.79 (d, J =3.6 Hz, 1 H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 Hz):  $\delta = 17.2$ , 20.8, 20.9, 29.9, 34.3, 40.2, 40.4, 60.5, 61.7, 77.0, 87.4, 125.9, 126.7, 127.1, 201.4 ppm. IR (neat):  $\tilde{v} = 2929$ , 1730, 1557, 1436, 1377, 1257, 1132 cm<sup>-1</sup>. HRMS calcd. for C<sub>17</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>S [M + H]<sup>+</sup> 355.1692; found 355.1692. HPLC Chiracel OD-H 90:10 (hexane/*i*PrOH), 254 nm, 0.5 mL min<sup>-1</sup>, retention time 16.6 min (minor) and 20.2 min (major).

**3-Cyclopropyl-4-nitro-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)butanal (7b):** The representative experimental procedure was applied to compound **7a** (48 mg, 0.5 mmol) for 4 h to yield product **7b** (100 mg, 64%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta = 0.26$  (s, 2 H), 0.58 (d, J = 7.6 Hz, 2 H), 0.76 (t, J = 3.6 Hz, 1 H), 1.11–1.55 (m, 18 H), 2.05 (m, 1 H), 4.33 (s, 1 H), 4.55 (m, 1 H), 4.64 (m, 1 H), 9.93 (t, J = 2.2 Hz, 1 H), 10.22 (s, 1 H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 Hz):  $\delta = 3.5$ , 4.3, 4.6, 4.8, 9.2, 10.2, 16.6, 20.0, 20.1, 33.6, 34.0, 39.5, 39.8, 44.0, 46.3, 59.6, 61.1, 76.3, 76.5, 86.1, 86.6, 201.5, 204.0 ppm. IR (neat):  $\tilde{v} = 2940$ , 1725, 1551, 1433, 1376, 1256, 1132, 745 cm<sup>-1</sup>. HRMS calcd. for C<sub>16</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub> [M + H]<sup>+</sup> 313.2127; found 313.2127. HPLC: Chiracel OD-H 99:1 (hexane/*i*PrOH), 254 nm, 0.5 mL min<sup>-1</sup>, retention time 13.9, 15.1 min (minor) and 15.7, 18.8 min(major).

General Procedure for the Tandem Diethyl Malonate/TEMPO Addition: A mixture of aldehyde (0.25 mmol), diethyl malonate (3 equiv.), TEMPO (2 equiv.), adamantanecarboxylic acid (10 mol-%), and (S)-2-[diphenyl(trimethylsilyloxy)methyl]pyrrolidine (20 mol-%) in CH<sub>3</sub>CN (0.4 M) was stirred. The solvent was removed with a rotary evaporator to produce a residue, which was purified by column chromatography on a silica gel with elution with hexane and ether.

**Diethyl 2-[3-Oxo-1-phenyl-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)propyl]malonate (1c):** The representative experimental procedure was applied to compound **1a** (33 mg, 0.25 mmol) for 20 h to yield product **1c** (95 mg, 80%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 0.90– 0.96 (m, 6 H), 1.06 (s, 3 H), 1.20–1.22 (m, 6 H), 1.28 (m, 5 H), 1.40 (m, 4 H), 3.84–3.91 (m, 1 H), 4.00 (m, 2 H), 4.22 (m, 2 H), 4.46– 4.49 (m, 1 H), 7.20–7.28 (m, 5 H), 9.68 (d, *J* = 4.8 Hz, 1 H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 Hz):  $\delta$  = 13.9, 14.3, 17.2, 20.7, 34.2, 34.3, 40.3, 40.4, 46.5, 53.8, 60.1, 61.5, 62.0, 87.6, 127.7, 128.2, 129.3, 135.5, 167.1, 167.7, 204.0 ppm. IR (neat):  $\tilde{v}$  = 2936, 1735, 1455, 1375, 1259, 1181, 1029, 702 cm<sup>-1</sup>. HRMS calcd. for C<sub>25</sub>H<sub>37</sub>NO<sub>6</sub> [M + H]<sup>+</sup> 448.2699; found 448.2699. HPLC Chiracel AD-H 95:5 (hexane/*i*PrOH), 210 nm, 0.5 mL min<sup>-1</sup>, retention time 12.9 min (minor) and 16.7 min (major).

**Diethyl 2-[3-Oxo-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)-1-***p***-tol-ylpropyl|malonate (2c):** The representative experimental procedure was applied to compound **2a** (37 mg, 0.25 mmol) for 24 h to yield product **2c** (85 mg, 74%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta = 0.93$ – 0.98 (m, 6 H), 1.06 (s, 3 H), 1.19–1.29 (m, 12 H), 1.40–1.41 (m, 3 H), 2.28 (s, 3 H), 3.85–3.93 (m, 2 H), 3.95–3.97 (m, 2 H), 4.20–4.25 (m, 2 H), 4.44–4.47 (m, 1 H), 7.04–7.09 (m, 4 H), 9.65 (d, *J* = 5.2 Hz, 1 H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 Hz):  $\delta = 13.9$ , 14.2, 17.2, 20.8, 21.3, 29.9, 34.2, 34.3, 40.2, 40.4, 46.0, 54 0, 60.1, 61.4, 61.9, 87.8, 128.9, 129.1, 132.3, 37.2, 167.1, 167.7, 203.7 ppm. IR (neat):  $\tilde{v} = 786$ , 1028, 1180, 1368, 1465, 1735, 2935 cm<sup>-1</sup>. HRMS calcd. for C<sub>26</sub>H<sub>39</sub>NO<sub>6</sub> [M + H]<sup>+</sup> 462.2856; found 462.2856. HPLC Chiracel AD-H 95:5 (hexane/*i*PrOH), 210 nm, 0.5 mL min<sup>-1</sup>, retention time 13.8 min (minor) and 17.7 min (major).

**Diethyl 2-[1-(4-Methoxyphenyl)-3-oxo-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)propyl]malonate (3c):** The representative experimental procedure was applied to compound **3a** (41 mg, 0.25 mmol) for 18 h to yield product **3c** (92 mg, 77%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 0.94–0.99 (m, 6 H), 1.06 (s, 3 H), 1.19–1.28 (m, 12 H), 1.40 (m, 3 H), 3.76 (s, 3 H), 3.88–3.92 (m, 4 H), 4.20–4.25 (m, 2 H), 4.44–4.46 (m, 1 H), 6.79 (d, *J* = 8.8 Hz, 2 H), 7.13 (d, *J* = 8.8 Hz, 2 H), 9.65 (d, *J* = 5.2 Hz, 1 H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 Hz):  $\delta$  = 13.9, 14.2, 17.2, 20.7, 34.2, 34.3, 40.2, 40.4, 45.6, 54.1, 55.3, 61.5, 61.9, 87.7, 113.6, 127.3, 130.3, 158.8, 167.2, 167.7, 203.7 ppm. IR (neat):  $\tilde{v}$  = 2935, 1734, 1515, 1374, 1253, 1182, 1033, 832 cm<sup>-1</sup>. HRMS calcd. for C<sub>26</sub>H<sub>39</sub>NO<sub>7</sub> [M + H]<sup>+</sup> 478.2805; found 478.2805. HPLC Chiracel AD-H 95:5 (hexane/*i*PrOH), 210 nm, 0.5 mL min<sup>-1</sup>, retention time 20.7 min (minor) and 31.9 min (major).

Diethyl 2-[1-(Naphthalen-2-yl)-3-oxo-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)propyl|malonate (4c): The representative experimental procedure was applied to compound 4a (45 mg, 0.25 mmol) for 48 h to yield product 4c (72 mg, 57%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 1.33 (m, 4 H), 1.15–1.25 (m, 11 H), 0.98 (s, 3 H), 0.86 (s, 3 H), 0.75 (t, J = 7.2 Hz, 3 H), 3.74 (m, 2 H), 4.05 (d, J =10.8 Hz, 1 H), 4.15 (m, 3 H), 4.49 (m, 1 H), 7.30 (d, J = 8 Hz, 1 H), 7.36 (m, 2 H), 7.58 (s, 1 H), 7.69 (m, 3 H), 9.64 (d, J = 4.8 Hz, 1 H), 9.71 (d, J = 4.8 Hz, 1 H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 Hz):  $\delta = 13.9, 14.3, 17.3, 20.9, 30.0, 34.3, 34.4, 40.3, 40.5, 46.6, 53.9,$ 60.2, 61.6, 62.0, 87.7, 126.0, 126.1, 127.3, 127.6, 127.8, 127.9, 128.3, 132.7, 133.0, 133.3, 167.2, 167.7, 204.0 ppm. IR (neat):  $\tilde{v} = 2978$ , 2933, 1732, 1733, 1259, 1185, 751 cm<sup>-1</sup>. HRMS calcd. for  $C_{29}H_{39}NO_6 \ [M + H]^+ 498.2856$ ; found 489.2852. HPLC Chiracel AD-H 95:5 (hexane/iPrOH), 210 nm, 0.5 mL min<sup>-1</sup>, retention time 18.2 min (minor) and 28.0 min (major).

**Diethyl 2-[1-(4-Nitrophenyl)-3-oxo-2-(2,2,6,6-tetramethylpiperidim-1-yloxy)propyl]malonate (5c):** The representative experimental procedure was applied to compound **5a** (44 mg, 0.25 mmol) for 72 h to yield product **5c** (113 mg, 91%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta = 0.99$  (m, 10 H), 1.25 (m, 11 H), 1.37 (m, 4 H), 3.91 (m, 2 H), 4.01 (m, 1 H), 4.12 (m, 1 H), 4.21 (m, 2 H), 4.53 (m, 1 H), 7.42 (d, J = 0.02 Hz, 2 H), 8.14 (d, J = 8.8 Hz, 2 H), 9.73 (d, J = 4.4 Hz, 1 H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 Hz):  $\delta = 14.0$ , 14.2, 17.2, 21.0, 34.2, 34.3, 40.3, 40.5, 46.3, 53.0, 60.4, 61.7, 61.9, 62.3, 86.7, 123.4, 130.3, 143.8, 147.2, 147.2, 166.7, 167.2, 203.6 ppm. IR (neat):  $\tilde{v} = 2979$ , 2934, 1733, 1524, 1466, 1348, 1259, 1181, 856 cm<sup>-1</sup>. HRMS calcd. for C<sub>25</sub>H<sub>36</sub>N<sub>2</sub>O<sub>8</sub> [M + H]<sup>+</sup> 493.2550; found 493.2550. HPLC Chiracel AD-H 85:15 (hexane//PrOH), 210 nm, 0.5 mLmin<sup>-1</sup>, retention time 22.3 min (minor) and 36.6 min (major).

# FULL PAPER

**Diethyl 2-[3-Oxo-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)-1-**(**thiophen-2-yl)propyl]malonate (6c):** The representative experimental procedure was applied to compound **6a** (35 mg, 0.25 mmol) for 48 h to yield product **6c** (113 mg, 99%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta$  = 1.08 (10 H), 1.21 (s, 4 H), 1.29 (m, 8 H), 1.42 (m, 5 H), 4.01 (m, 3 H), 4.22 (m, 2 H), 4.32 (m, 1 H), 4.49 (t, *J* = 5.6 Hz, 1 H), 6.86 (m, 1 H), 6.90 (m, 1 H), 7.18 (d, *J* = 4.8 Hz, 1 H), 9.70 (d, *J* = 4.4 Hz, 1 H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 Hz):  $\delta$  = 203.4, 167.3, 166.9, 137.4, 126.8, 126.4, 125.1, 86.9, 62.0, 61.7, 61.3, 60.2, 54.3, 41.4, 40.4, 40.2, 34.3, 20.8, 17.2, 14.2, 13.9 ppm. IR (neat):  $\tilde{v}$  = 2979, 2934, 1734, 1635, 1366, 1259, 1183, 701 cm<sup>-1</sup>. HRMS calcd. for C<sub>23</sub>H<sub>35</sub>NO<sub>6</sub>S [M + H]<sup>+</sup> 454.2263; found 454.2263. HPLC Chiracel AD-H 93:7 (hexane/EtOH), 210 nm, 0.5 mLmin<sup>-1</sup>, retention time 10.6 min (minor) and 14.4 min (major).

**Diethyl 2-[1-Cyclopropyl-3-oxo-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)propyl]malonate (7c):** The representative experimental procedure was applied to compound **7a** (24 mg, 0.25 mmol) for 24 h to yield product **7c** (45 mg, 44%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta = 0.22$  (m, 2 H), 0.48 (m, 2 H), 0.92 (m, 1 H), 1.11 (d, J = 8.4 Hz, 7 H), 1.18 (d, J = 8 Hz, 6 H), 1.26 (m, 6 H), 1.42 (m, 6 H), 1.95 (m, 1 H), 3.77 (d, J = 7.2 Hz, 1 H), 4.20 (m, 4 H), 4.39 (m, 1 H), 9.85 (m, 1 H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 Hz):  $\delta = 203.4$ , 168.8, 168.4, 88.7, 61.8, 61.6, 60.2, 53.3, 45.3, 40.6, 40.3, 34.9, 34.3, 20.9, 7.5, 14.5, 10.9, 5.6, 5.2 ppm. IR (neat):  $\tilde{v} = 2935$ , 1732, 1466, 1372, 1146 cm<sup>-1</sup>. HRMS calcd. for C<sub>22</sub>H<sub>37</sub>NO<sub>6</sub> [M + H]<sup>+</sup> 412.2699; found 412.2699. HPLC Chiracel AS-H 99:1 (hexane/EtOH), 210 nm, 0.5 mL min<sup>-1</sup>, retention time 10.2 min (major) and 11.9 min (minor).

**Diethyl 2-[1-(4-Bromophenyl)-3-oxo-2-(2,2,6,6-tetramethylpiperidin-1-yloxy)propyl]malonate (8c):** The representative experimental procedure was applied to compound **8a** (53 mg, 0.25 mmol) for 48 h to yield product **8c** (73 mg, 55%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):  $\delta = 0.96-1.00$  (m, 6 H), 1.06 (s, 3 H), 1.19–1.22 (m, 6 H), 1.25–1.28 (m, 5 H), 1.41 (m, 4 H), 3.90–3.93 (m, 2 H), 3.97 (d, J = 2.8 Hz, 2 H), 4.19–4.25 (m, 2 H), 4.46 (m, 1 H), 7.09 (d, J = 8.4 Hz, 2 H), 7.38 (d, J = 8.4 Hz, 2 H), 9.68 (d, J = 4.8 Hz, 1 H) ppm. <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 Hz):  $\delta = 13.9$ , 14.2, 17.2, 20.7, 34.2, 34.3, 40.2, 40.4, 45.9, 53.4, 60.2, 61.6, 62.0, 87.1, 121.7, 130.9, 131.3, 134.8, 166.9, 167.4, 203.7 ppm. IR (neat):  $\tilde{v} = 3054$ , 2986, 1422, 1265, 747 cm<sup>-1</sup>. HRMS calcd. for C<sub>25</sub>H<sub>36</sub>BrNO<sub>6</sub> [M + H]<sup>+</sup> 526.1802; found 526.1802. HPLC Chiracel AD-H 95:5 (hexane/*i*PrOH), 210 nm, 0.5 mL min<sup>-1</sup>, retention time 18.6 min (minor) and 29.0 min (major).

Ethyl 1-Benzyl-4-(4-bromophenyl)-2-oxo-5-(2,2,6,6-tetramethylpiperidin-1-yloxy)piperidine-3-carboxylate (8d): The mixture of 8c (55 mg, 0.104 mmol), sodium cyanoborohydride (0.135 mmol), benzylamine (0.156 mmol), and acetic acid (2-3 drops) in dioxane (5 mL) was stirred at 40 °C for 18 h to yield 8d (39.3 mg, 66%). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.43 (d, J = 8.5 Hz, 2 H), 7.32 (m, 5 H), 7.20 (d, J = 8.5 Hz, 2 H), 5.40 (d, J = 14.5 Hz, 1 H), 4.32 (s, 1 H), 4.21 (d, J = 12.0 Hz, 1 H), 4.11 (m, 2 H), 3.87 (dd, J = 14.0, 1.0 Hz, 1 H), 3.77 (d, J = 14.0 Hz, 1 H), 3.57 (dd, J = 12.5, 2.0 Hz, 1 H), 3.27 (dd, J = 13.5, 3.5 Hz, 1 H), 1.22–1.49 (m, 6 H), 1.13 (t, *J* = *J* = 7.0 Hz, 3 H), 1.07 (s, 3 H), 0.95 (s, 3 H), 0.78 (s, 3 H), 0.64 (s, 3 H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 169.9, 166.0, 137.2, 136.2, 131.3, 130.3, 128.7, 128.5, 127.6, 121.2, 76.0, 61.3, 59.7, 50.3, 49.4, 48.9, 45.4, 40.6, 40.4, 34.1, 32.5, 21.1, 20.6, 16.9, 14.0 ppm. HRMS calcd. for  $C_{30}H_{39}N_2O_4 [M + H]^+ 573.2156$ ; found 573.2175. IR (neat):  $\tilde{v} = 2930, 1737, 1649, 1490, 1368, 1241$ , 1152, 1075, 1010 cm<sup>-1</sup>.

Supporting Information (see footnote on the first page of this article): Copies of <sup>1</sup>H NMR, <sup>13</sup>C NMR, and HPLC spectra for **1b–7b**, **1c–8c**, and **8d**.

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Iminium/Cu Catalysis

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