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Synthesis of Pyrrolin-4-ones by Pt-Catalyzed Cycloisomerization in PEG under Microwaves

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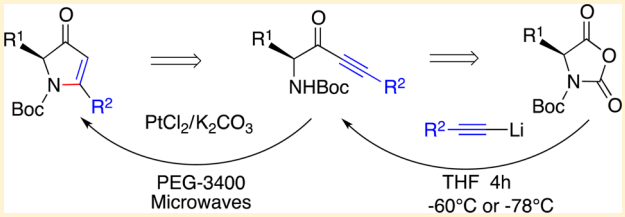
Supporting Information

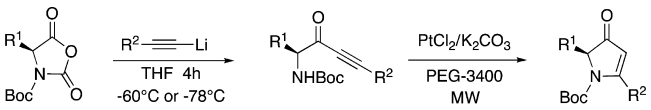
ABSTRACT: The unprecedented eco-friendly Pt-catalyzed 5-*endo-dig* cycloisomerization of readily available α-amino ynones is reported under microwave irradiation in PEG-3400 as reaction matrix. The corresponding pure pyrrolin-4-ones were obtained in excellent yields (80−98%) directly after a straightforward precipitation−filtration workup, thus avoiding any chromatographic purification. The catalytic system was recycled and the chiral purity of all the products was also investigated.



The field of environmentally friendly (or green) chemistry is currently attracting increasing attention.[1] One important area in current chemical science is to develop mild and sustainable processes to prepare organic molecules. Previous work developed in our laboratory made use of poly(ethylene glycol) (PEG)[2] as an alternative and eco-compatible solvent under microwave irradiation.[3] In the past decades, the use of transition-metal catalysis to provide new reactivities of organic substrates has emerged.[4] The metal-catalyzed cycloisomerization is now commonly used for the synthesis of numerous families of heterocycles,[5] and several strategies have been also developed in our laboratories.[3f,g,6]

Starting from α-amino ynones **1**, easily obtained from the addition to organolithium reagents to urethane-protected *N*-carboxyanhydrides[3g] (UNCAs), pyrrolin-4-ones **2** were synthetized by an unprecedented platinum-catalyzed cycloisomerization reaction under mild conditions (Scheme 1).

Scheme 1. Platinum-Catalyzed Cycloisomerization Reaction of 1 Using PEG-3400 as a Green Solvent under Microwaves



UNCA 1 2

A pyrrolinone scaffold similar to **2** is present in diverse pharmaceutically active compounds,[7] and various families of nitrogen-containing heterocycles[8] can be easily obtained by simple transformation of α-amino ynones **1**. However, straightforward procedures to pyrrolinones were poorly investigated in the past, and only rare examples are reported where ynones **1** were used as substrates in toxic mercury(II)- or gold(III)-catalyzed heterocyclization in volatile organic solvents under reflux.[9−11] In most of the cases, the yields were good, but the enantiomeric excess was not always satisfying and no recycling experiments of the catalyst were performed. In order to alleviate the potential loss of chiral integrity, we initiated a study with metals other than mercury or gold. α-Amino ynone **1a**[3g] served as a model to study the cycloisomerization reaction using various PEG-3400/metal catalyst associations under microwaves in order to compare conversions, yields, and chiral integrity (Table 1). Microwave activation (monomode waves) is particularly adapted in the reactions using solid PEG since the focused heating generated by the microwaves together with the good absorption of the PEG quickly provides a liquid-phase environment once PEG is melted (above 50 °C).[2b] The viscosity of the reaction medium remains high, but microwaves provide a homogeneous heating.

From the various metals which were studied (Table 1), the complete conversion of substrate **1a** was possible only when $PtCl_2$ was the catalyst, leading to pyrrolinone **2a** with an excellent yield after 30 min. The amount of catalyst was reduced from 5 to 1 mol % (Table 1, entry 5) resulting in an increase of the yield of the reaction. Unfortunately, it was difficult to reproduce the results with such a small amount of catalyst, and the study was carried out on a 5 mol % basis. In both cases, however, the enantiomeric ratio was affected, dropping from 90/10 of the starting material to 68/32 (Table 1, entries 5 and 6). The epimerization could be due to the keto−enol equilibrium favored by the presence of HCl released during the reaction.[11,12] In order to neutralize the acid formed

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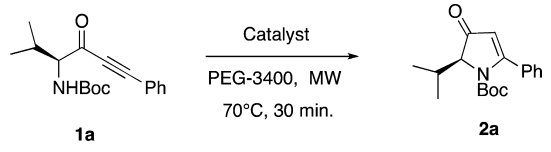
Table 1. Screening of Different Catalysts for the Cycloisomerization Reaction of 1a[a]



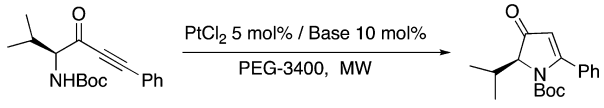
1a 2a

entry	catalyst (mol %)	conversion[b] (%)	yield[c] (%)	er[d] (%)
1[e]	–	0	0	–
2	CuO (5)	0	0	–
3	$CuCl_2$ (5)	90	75	57/43
4	PdI_2(2)	21	30	nd
5	$PtCl_2$(1)	100	99	68/32
6	$PtCl_2$ (5)	100	95	68/32

[a]Enantiomeric ratio (er) of **1a** is 90/10. [b]Conversions were determined by HPLC. [c]Yields were calculated by ^{1}H NMR using CH_2Br_2 as an internal standard. [d]Enantiomeric ratio (er) was determined by chiral HPLC analyses. [e]Reaction was carried out for 60 min.

in situ and to slow down the epimerization process, different combinations of platinum(II) dichloride and various bases were tested, and a selection of results is summarized in Table 2.

Table 2. $PtCl_2$-Catalyzed Cycloisomerization Reaction of α-Amino Ynone 1a in Basic Medium



1a 2a

entry	base	T (°C)	time (min)	er 1a[a] (%)	er 2a[a] (%)	yield[b] (%)
1	Cs_2CO_3	70	60	90/10	74/26	81
2	$NaHCO_3$	70	30	90/10	80/20	87
3	Et_3N	70	60	90/10	79/21	83
4	*t*-BuOK	70	60	90/10	59/41	54
5[c]	K_2CO_3	80	60	90/10	–	0
6	K_2CO_3	80	30	90/10	86/14	70
7	K_2CO_3	70	30	90/10	89/11	90

[a]Enantiomeric ratio (er) was determined by chiral HPLC analyses. [b]Yields were calculated by ^{1}H NMR using CH_2Br_2 as an internal standard. [c]The reaction was carried out in the absence of catalyst.

When Cs_2CO_3, Et_3N, or *t*-BuOK (Table 2, entries 1, 3, and 4) was used, the reaction time was longer and full conversion of substrate **1a** was complete after 60 min. Furthermore, the enantiomeric excess of product **2a** was decreased (18–60%), while in the absence of catalyst the cyclization did not take place (Table 2, entry 5). Under the optimized reaction conditions (Table 2, entry 7), the starting enantiomeric ratio in **1a** was preserved in the final product **2a**, which could be easily recovered as a pure compound after a practical and simple precipitation/filtration workup. The crude was dissolved in a small amount of dichloromethane and then precipitated in Et_2O. After filtration to separate PEG-based solids, pure product **2a** was recovered in 94% yield after evaporation of the filtrate. In some cases, an aqueous washing to remove traces of PEG was necessary. Compared to other procedures,[11] no column chromatography was required decreasing the use of organic solvent (limited to the precipitation procedure). Various α-amino ynones **1a–h** were reacted under the optimized conditions to afford the corresponding pyrrolinones **2a–h** always in excellent isolated yields (90–98%) and with good to excellent preservation of the enantiomeric ratio (Table 3). As described previously in the literature,[11] the epimerization was very limited for the hindered substrates (Table 3, entries 1–3). In the case of less hindered substrates, epimerization occurred but was restrained compared to the one observed with a gold catalyst.[11]

The recyclability of the catalytic system PEG-3400/$PtCl_2$/K_2CO_3 was also investigated for the first time in this type of transformation. Two sets of experiments were carried out on two different α-amino ynones **1b** and **1c**. After a first run (performed as described in Table 2) on each of the starting materials (Table 4, entries 1 and 3), the valine-based pyrrolinones **2b** and **2c** were obtained in very good yield and retention of stereochemistry after precipitation. The precipitate recovered after the precipitation–filtration workup for each experiment was reused[3] in the next runs (Table 4, entries 2 and 4) by charging the reaction vessel with **1b** or **1c**, respectively, to provide again **2b** or **2c**, respectively, with high yields and preservation of the starting optical purity. One more run could be efficiently performed on **1c** (Table 4, entry 5) but not on **1b**, which remained unreacted in the next cycle.

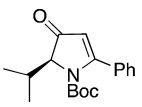
In conclusion, we disclose herein a new route to the synthesis of pyrrolin-4-ones using unprecedented Pt-catalyzed 5-*endo*-*dig* cycloisomerization of readily available α-amino ynones **1**[3g] in PEG-3400 as an alternative and eco-friendly solvent under microwave irradiation. The final products were always recovered in excellent yields and purity without any time- or solvent-consuming column chromatography after a simple precipitation–filtration workup that allowed catalytic system recovering and recycling.

EXPERIMENTAL SECTION

Typical Procedure for the $PtCl_2$-Catalyzed Heterocyclization of α-Amino Ynones 1a–h. A mixture of $PtCl_2$ (1.3 mg, 0.005 mmol), K_2CO_3 (1.4 mg, 0.01 mmol), PEG-3400 (400 mg), and α-amino ynones **1**[3g] (0.1 mmol) placed in a sealed vessel was heated at 70 °C under microwave irradiation (initial power 400 W) for 30 min. The reaction mixture was solubilized in a small amount of CH_2Cl_2 (2.0 mL) and precipitated in Et_2O (250 mL). After 3 h at −18 °C, filtration of the catalytic system (PEG-3400/Pt/base) and evaporation of diethyl ether afforded pure product **2**. When necessary, an aqueous washing to remove traces of PEG was performed.

Typical Procedure to Recycle the Catalytic System. α-Amino ynone **1** (0.1 mmol) was added to the precipitate PEG-3400/Pt/base obtained after the precipitation–filtration workup from a previous experiment (Table 4) and placed in a sealed vessel then heated up using microwave irradiation (initial power 400W) at 70 °C (the instrument adjusted the heating power to keep this temperature constant) for the indicated time (Table 4), to afford pure product **2** after precipitation/filtration workup as previously described.[3]

2-Isopropyl-3-oxo-5-phenyl-2,3-dihydropyrrole-1-carboxylic Acid *tert*-Butyl Ester (2a).



Starting from **1a** (24.1 mg, 0.08 mmol), 22.6 mg was obtained (94% isolated yield): CAS Registry No. 1169845-39-9; yellow solid; mp 65–68 °C (lit.[11] 70–72 °C; ee 90%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.36–7.34 (m, 5H), 5.53 (s, 1H), 4.11 (d, 1H, *J* = 3.5 Hz), 2.54 (septuplet, 1H, *J* = 3.5 Hz), 1.16 (s, 9H), 1.10 (d, 3H, *J* = 7.0 Hz), 0.95 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 201.1, 172.9, 150.3, 133.1, 130.2, 128.0, 127.0, 113.6, 82.6, 71.5, 32.1, 27.6, 17.2, 17.1; ESIMS *m*/*z* 302.1 $(M + H)^+$, 246.1 $(M + H - t\text{-Bu})^+$, 603.3

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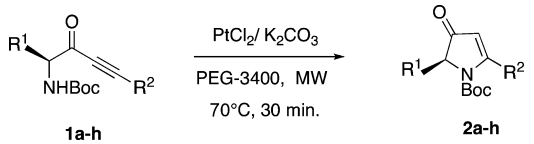
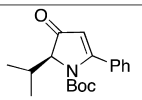
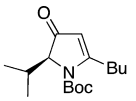
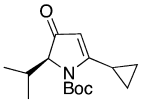
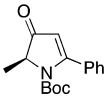
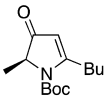
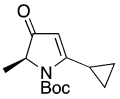
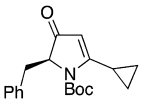
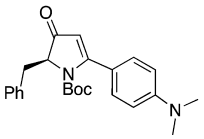
Table 3. Pt-Catalyzed Cycloisomerization of α-Amino Ynone Derivatives under Microwave Irradiation in PEG-3400

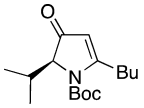


Entry	Product		Isolated yield of **2** (%)	*e.r.* (%) of **1**[a]	*e.r.* (%) of **2**[a]
1		**2a**	94	99/1	95/5
2		**2b**	95	98/2	97/3
3		**2c**	98	100/0	98/2
4		**2d**	90	83/17	74/26
5		**2e**	90	97/3	63/57
6		**2f**	98	95/5	86/14
7		**2g**	90	59/41	56/44
8		**2h**	90	98/2	79/21[b]

[a]Enantiomeric ratio (er) was determined by chiral HPLC analysis. [b]The reaction was carried out in the absence of base.

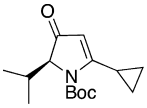
$(2M + H)^+$; HRMS (ESI) calcd for $C_{18}H_{24}NO_3$ $(M + H)^+$ 302.1756, found 302.1748; HPLC Chiralpak AD-H, 2-propanol/hexane = 2/98, flow rate 1.0 mL/min, λ = 214 *nm*, t_{major} = 9.333 min, t_{minor} = 8.417 min.

5-Butyl-2-isopropyl-3-oxo-2,3-dihydropyrrole-1-carboxylic Acid *tert*-Butyl Ester (2b).



Starting from **1b** (22.5 mg, 0.08 mmol), 21.1 mg was obtained (95% isolated yield): yellow oil, ee 97%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.34 (s, 1H), 3.96 (d, 1H, J = 3.4 Hz), 2.97−2.76 (m, 2H), 2.50−2.45 (m, 1H), 1.60−1.40 (m, 4H), 1.47 (s, 9H), 1.15 (d, 3H, J = 7.1 Hz), 0.95 (t, 3H, J = 7.0 Hz), 0.83 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 200.5, 177.0, 149.4, 110.1, 82.6, 70.2, 31.0, 30.6, 29.7, 28.0, 22.4, 17.3, 15.9, 13.7; ESIMS m/z 282.2 (M + H)$^+$, 304.2 (M + Na)$^+$, 226.2 (M + H − *t*-Bu)$^+$, 563.3 (2M + Na)$^+$; HRMS (ESI) calcd for $C_{16}H_{28}NO_3$ $(M + H)^+$ 282.2069, found 282.2063; HPLC Chiralpak AD-H, 2-propanol/hexane = 2/98, flow rate 1.0 mL/min, λ 214 *nm*, t_{major} = 6.833 min, t_{minor} = 4.817 min.

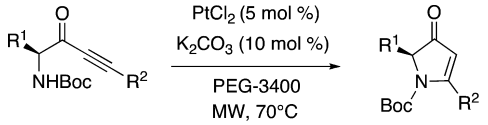
5-Cyclopropyl-2-isopropyl-3-oxo-2,3-dihydropyrrole-1-carboxylic Acid *tert*-Butyl Ester (2c).



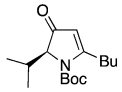
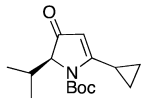
Starting from **1c** (26.5 mg, 0.1 mmol), 26.0 mg was obtained (98% isolated yield): yellow solid; mp 70−72 °C, ee 95%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.01 (s, 1H), 3.98 (d, 1H, J = 3.1 Hz), 2.74−2.65 (m, 1H), 2.52−2.42 (m, 1H), 1.53 (s, 9H), 1.17−1.13 (m, 2H), 1.14 (d, 3H, J = 7.0 Hz), 0.84−0.75 (m, 2H), 0.81 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 200.3, 179.7, 149.9, 105.0, 82.7, 70.8, 30.9, 28.2, 17.5, 16.1, 11.4, 11.3, 11.2; ESIMS m/z 266.2 (M +

dx.doi.org/10.1021/jo302474r | *J. Org. Chem.* 2013, 78, 2698−2702

Table 4. Recycling of the Catalytic System



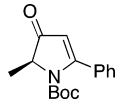
1b, c **2b, c**

Entry	Runs	Product	Time (min)	*e.r.* **1** (%)[a]	*e.r.* **2** (%)[a]	Conv. **1** (%)	Yield **2** (%)[b]
1	Run 1		30	98/2	97/3	100	94
2	Run 2	**2b**	45	98/2	97/3	100	94
3	Run1		30	100/0	98/2	100	98
4	Run 2		45	100/0	98/2	100	96
5	Run 3	**2c**	60	100/0	98/2	100	98

[a]Enantiomeric ratio (er) was determined by chiral HPLC analyses. [b]Conversion was determined by HPLC. [c]Isolated yields.

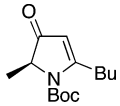
H)$^+$, 210.2 (M + H − *t*-Bu)$^+$, 531.4 (2M + H)$^+$; HRMS (ESI) calcd for $C_{15}H_{24}NO_3$ (M + H)$^+$ 266.1756, found 266.1761; HPLC Chiralpak AD-H, 2-propanol/hexane = 2/98, flow rate 1.0 mL/min, λ = 214 nm, t_{major} = 12.6 min, t_{minor} = 9.083 min.

2-Methyl-3-oxo-5-phenyl-2,3-dihydropyrrole-1-carboxylic Acid *tert*-Butyl Ester (2d).



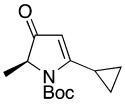
Starting from **1d** (27.4 mg, 0.1 mmol), 24.7 mg was obtained (90% isolated yield): CAS Registry No. 1169845-42-4; yellow solid; mp 80−85 °C (lit.[11] 90−92 °C); ee 48%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.46−7.41 (m, 5H), 5.58 (s, 1H), 4.24 (q, 1H, *J* = 7.1 Hz), 1.61 (d, 3H, *J* = 7.1 Hz), 1.29 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 201.0, 172.1, 149.7, 132.8, 130.2, 127.9, 127.4, 111.2, 82.8, 63.6, 27.8, 17.6; ESIMS *m*/*z* 274.2 (M + H)$^+$, 296.1 (M + Na)$^+$, 218 (M + H − *t*-Bu)$^+$, 174.2 (M + H − Boc)$^+$; HRMS (ESI) calcd for $C_{16}H_{20}NO_3$ (M + H)$^+$ 274.1443, found 274.1431; HPLC Chiralpak AD-H, 2-propanol/hexane = 2/98, flow rate 1.0 mL/min, λ = 214 nm, t_{major} = 11.483 min, t_{minor} = 10.917 min.

5-Butyl-2-methyl-3-oxo-2,3-dihydropyrrole-1-carboxylic Acid *tert*-Butyl Ester (2e).



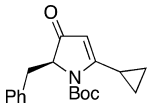
Starting from **1e** (30.1 mg, 0.1 mmol), 27.0 mg was obtained (90% isolated yield): yellow oil, ee 26%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.37 (s, 1H), 4.01 (q, 1H, *J* = 7.0 Hz), 2.92 (m, 2H), 1.60−1.39 (m, 4H), 1.49 (s, 9H), 1.40 (d, 3H, *J* = 7.0 Hz), 0.95 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 201.1, 176.7, 149.2, 107.9, 82.7, 62.7, 30.9, 29.5, 28.2, 22.4, 17.3, 13.8; ESIMS *m*/*z* 254.1 (M + H)$^+$, 276.1 (M + Na)$^+$, 198.1 (M + H − *t*-Bu)$^+$, 507.2 (2M + H)$^+$; HRMS (ESI) calcd for $C_{14}H_{24}NO_3$ (M + H)$^+$: 254.1756, found 254.1759. HPLC Chiralcel OD-H, 2-propanol/hexane = 2/98, flow rate 1.0 mL/min, λ = 214 nm, t_{major} = 7.7 min, t_{minor} = 6.983 min.

5-Cyclopropyl-2-methyl-3-oxo-2,3-dihydropyrrole-1-carboxylic Acid *tert*-Butyl Ester (2f).



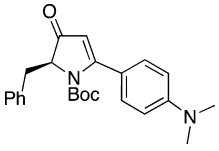
Starting from **1f** (23.7 mg, 0.1 mmol), 23.4 mg was obtained (98% isolated yield): yellow oil, ee 72%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 5.02 (s, 1H), 4.02 (q, 1H, *J* = 7.0 Hz), 2.83−2.74 (m, 1H), 1.54 (s, 9 Hz), 1.45 (d, 3H, *J* = 7.0 Hz), 1.21−1.16 (m, 2H), 0.87−0.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 200.6, 179.4, 149.6, 102.4, 82.8, 63.2, 28.2, 17.3, 11.9, 11.5, 11.1; ESIMS *m*/*z* 238.1 (M + H)$^+$, 260.2 (M + Na)$^+$, 182.1 (M + H − *t*-Bu)$^+$; HRMS (ESI) calcd for $C_{13}H_{20}NO_3$ (M + H)$^+$: 238.1443, found 238.1442; HPLC Chiralcel OD-H, 2-propanol/hexane = 2/98, flow rate 1.0 mL/min, λ = 214 nm, t_{major} = 10.683 min, t_{minor} = 9.317 min.

2-Benzyl-5-cyclopropyl-3-oxo-2,3-dihydropyrrole-1-carboxylic Acid *tert*-Butyl Ester (2g).



Starting from **1g** (25.0 mg, 0.08 mmol), 22.5 mg was obtained (90% isolated yield): yellow oil, ee 12%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.20−7.17 (m, 3H), 7.07−7.04 (m, 2H), 4.84 (s, 1H), 4.3 (dd, 1H, *J* = 2.6, 6.1 Hz), 3.44 (dd, 1H, *J* = 6.1, 13.4 Hz), 3.24 (dd, 1H, *J* = 2.6, 13.4 Hz), 2.48−2.42 (m, 1H), 1.61 (s, 9H), 1.02−0.93 (m, 1H), 0.96−0.84 (m, 1H), 0.62−0.59 (m, 1H), 0.15−0.07 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 199.7, 180.0, 149.6, 134.5, 129.7, 127.9, 126.8, 105.3, 83.0, 67.1, 36.8, 28.3, 11.3, 10.9, 9.9; ESIMS *m*/*z* 314.1 (M + H)$^+$, 336.0 (M + Na)$^+$, 258.1 (M + H − *t*-Bu)$^+$, 627.2 (2M + H)$^+$, 649.2 (2M + Na)$^+$; HRMS (ESI) calcd for $C_{19}H_{24}NO_3$ (M + H)$^+$ 314.1756, found 314.1762; HPLC Chiralcel AD-H, 2-propanol/hexane = 2/98, flow rate 1.0 mL/min, λ = 214 nm, t_{major} = 16.443 min, t_{minor} = 12.917 min.

2-Benzyl-5-(4-dimethylaminophenyl)-3-oxo-2,3-dihydropyrrole-1-carboxylic Acid *tert*-Butyl Ester (2h).



Starting from **1h** (21.0 mg, 0.5 mmol), 17.7 mg was obtained (90% isolated yield): orange oil; ee 57%; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 7.20−7.16 (m, 5H), 7.02 (d, 2H, *J* = 8.9 Hz), 6.58 (d, 2H, *J* = 8.9 Hz), 5.35 (s, 1H), 4.42 (dd, 1H, *J* = 2.8, 6.9 Hz), 3.54 (dd, 1H, *J* = 6.3, 13.3 Hz), 3.35 (dd, 1H, *J* = 2.8, 13.3 Hz), 2.98 (s, 6H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm) 199.2, 174.0, 151.9, 150.2, 135.1, 129.9, 128.0, 126.8, 118.9, 111.1, 110.5, 82.5, 67.6, 40.1, 37.5, 28.0; ESIMS *m*/*z* 393.2 (M + H)$^+$, 337.1 (M + H − *t*-Bu)$^+$; HRMS (ESI) calcd for $C_{24}H_{29}N_2O_3$ (M + H)$^+$ 393.2178, found 393.2168; HPLC Chiralpak AD-H, 2-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 214 nm, t_{major} = 9.667 min, t_{minor} = 8.45 min.

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■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra and chiral HPLC chromatograms for compounds **2a−h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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