Tetrahedron Letters 50 (2009) 3363–3365

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Co-catalyst enhancement of enantioselective PTC Michael additions involving glycine imines

Barry Lygo [a,*], Christopher Beynon [a], Christopher Lumley [a], Michael C. McLeod [a], Charles E. Wade [b]

[a] School of Chemistry, University of Nottingham, Nottingham NG7 2RD, UK
[b] GlaxoSmithKline, Gunnels Wood Road, Stevenage, Herts SG1 2NY, UK

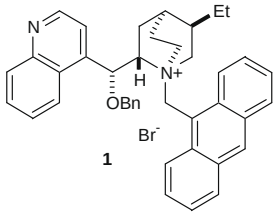
ARTICLE INFO

Article history:
Received 22 December 2008
Revised 5 February 2009
Accepted 16 February 2009
Available online 21 February 2009

ABSTRACT

In this Letter we demonstrate that the use of 2,4,6-trimethylphenol (mesitol) as a co-catalyst facilitates highly enantioselective addition of benzophenone glycine imine *tert*-butyl ester to a range of Michael acceptors.

In recent years, a number of chiral quaternary ammonium phase transfer catalysts (PTCs) have been found to promote highly enantioselective alkylation of glycine imine **2**.[1,2] This has led to the development of effective methods for the synthesis of a wide range of α-amino acid derivatives.[3] The corresponding reactions of imine **2** with Michael acceptors have proved to be more challenging.[4–6] These often result in lower enantioselectivities and lower yields than the corresponding alkylations.



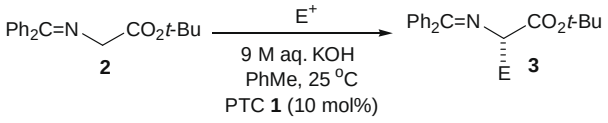
1

For example, we have found that the cinchona alkaloid-derived PTC **1** will promote highly enantioselective asymmetric alkylations of imine **2** with a wide range of alkyl halides.[7] However, under the same conditions, Michael acceptors such as methyl vinyl ketone (MVK) and *tert*-butyl acrylate give disappointing results (Table 1).

Clearly the differing transition states for these processes could account for these observations, but an additional factor may be that the Michael additions can also proceed via base-catalyzed (non-selective) background pathways.

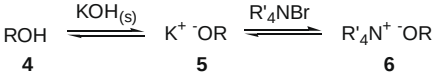
We considered that it might be possible to control the latter by employing a quaternary ammonium salt catalyst with a basic counterion (e.g., $R'_4\ N^+\ ^-OR$).[8] In this instance, it should be unnecessary to add additional base, and hence background reaction pathways should be minimized. This approach has so far been unsuccessful, mainly due to difficulties in isolating and purifying quaternary ammonium salts with appropriate basic counterions. As a result, we decided to investigate the possibility of generating $R'_4\ N^+\ ^-OR$ species **6** in situ. In principle this should be possible simply by mixing an alkoxide (e.g., KOR, **5**) with a quaternary ammonium salt such as **1**. As long as the alkoxide is sufficiently lipophilic the ion exchange equilibrium should favour the desired ion-pair combination. To further simplify the experimental protocol we envisaged that the alkoxide species might also be generated in situ by reaction of the corresponding alcohol (ROH, **4**) with KOH (Scheme 1). The advantage of this approach is that the quaternary ammonium alkoxide need never be isolated, but it suffers from the potential disadvantage that both KOH and KOR could promote non-selective Michael addition.

Table 1
Alkylation versus Michael addition of imine **2**



Electrophile	Yield[a] (%)	ee[b] (%)
$PhCH_2Br$	93	94 (*S*)
n-BuI	88	93 (*S*)
MVK	87	12 (*S*)
t-Butyl acrylate	<10	–

[a] Determined by ^1H NMR.
[b] Determined by HPLC.



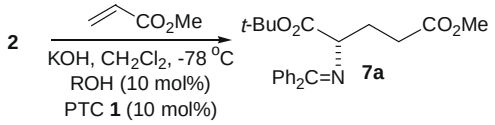
4 **5** **6**

Scheme 1. In situ generation of $R'_4\ N^+\ ^-OR$ species.

* Corresponding author. Tel.: +44 0 115 9513526; fax: +44 0 115 9513564.
E-mail address: b.lygo@nottingham.ac.uk (B. Lygo).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.02.123

Table 2
Effect of phenol additives on the enantioselective Michael addition of imine **2** to methyl acrylate



ROH	Time (h)	Yield[a] (%)	ee[b] (%)
None	24	<10[c]	—
Phenol	10	40[c]	81
4-Methylphenol	10	93	92
2,6,-Dimethylphenol	10	93	98
Mesitol	8	95	98
2,4,6-Tri-*tert*-butylphenol	10	82	91

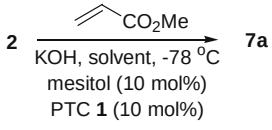
[a] Determined by ^{1}H NMR.
[b] Determined by HPLC.
[c] Conversion after 10 h by ^{1}H NMR.

To probe this further we decided to investigate the application of this approach in the Michael addition of imine **2** to methyl acrylate. We were able to establish that this reaction was not promoted by 10 mol % PTC **1** in conjunction with solid KOH[9] at −78 °C. However, if 10 mol % phenol was included, the resulting mixture was capable of promoting the desired Michael addition. After 10 h, the reaction had proceeded to 40% conversion and the resulting adduct **7a** was produced in 81% ee. In an effort to improve on this, a range of other phenol additives were examined (Table 2). This study identified mesitol (2,4,6-trimethylphenol) as a highly effective co-catalyst[10,11] for the Michael addition, generating the product **7a** in 95% yield and 98% ee.

Further investigation into the reaction conditions established that for reproducible results, the three catalyst components (KOH, mesitol and PTC **1**) need to be pre-mixed at 0 °C for 30 min. In addition, all three are required to be present during the Michael addition. If the solid KOH is removed prior to addition of imine **2** and methyl acrylate, then low conversions are observed. This suggests that the reaction mechanism is not as simple as initially envisaged.

As we have previously found that the nature of the solvent can have profound effects on quaternary ammonium salt-catalyzed Michael additions,[4e,12] we next investigated the effect of changing the reaction solvent (Table 3).

Table 3
Effect of solvent on the enantioselective Michael addition of imine **2** to methyl acrylate



Solvent	Time (h)	Yield[a] (%)	ee[b] (%)
CH_2Cl_2	8	95	98
PhMe	10	<10[c]	—
i-Pr_2O	10	<10[c]	—
THF	7	89	0
t-BuOMe	3	68	0
TAME[d]	10	32[c]	0
1,3-Dioxolane	3	85	34
CH_2Cl_2/PhMe (1:1)	10	90[c]	98
t-BuOMe/PhMe (1:1)	10	50[c]	−30

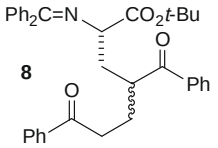
[a] Determined by ^{1}H NMR.
[b] Determined by HPLC.
[c] Conversion after 10 h by ^{1}H NMR.
[d] TAME = *tert*-amylmethylether.

Of the solvents investigated, only CH_2Cl_2, THF and 1,3-dioxolane gave complete reaction within 10 h at −78 °C, and of these, only CH_2Cl_2 resulted in high enantioselectivity. The majority of the other solvents gave either no reaction or a racemic product. In the case of *t*-BuOMe, the reaction was found to proceed significantly faster than in other solvents. This was found to be due to a fast background reaction mediated by the potassium salt of mesitol. It was also found that use of CH_2Cl_2/PhMe (1:1) resulted in similar levels of enantioselectivity to CH_2Cl_2 alone, but the rate of reaction was slowed. Interestingly, when *t*-BuOMe/PhMe (1:1) was used the opposite enantiomer of **7a** was produced in 30% ee.

These results clearly indicate that CH_2Cl_2 is the best solvent for this process, so we next moved on to probe the scope of this process by investigating the reaction of imine **2** with other Michael acceptors (Table 4).

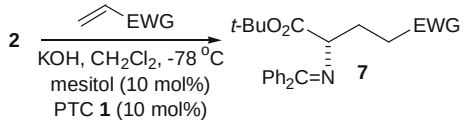
It was found that the optimized reaction conditions would successfully promote addition of imine **2** to a range of enones (Table 4, entries b–e) as well as acrylonitrile (entry f) and phenyl vinyl sulfone (entry g). Addition to the less electrophilic vinylphosphonates and amides was not successful, even at higher temperatures. In all cases, the levels of enantioselectivity were high.

Under the standard conditions, reaction with phenyl vinyl ketone (entry e) gave significant amounts of the double addition product **8**. This could be minimized by slow addition of the enone to the reaction mixture. Similar improvements to the yield of the acrylonitrile adduct **7f** could also be achieved via slow addition of the electrophile.



The absolute stereochemistry of product **7a** was established as (*S*) by conversion to *tert*-butyl pyroglutamate and comparison of the sign of rotation with that previously published.[16] We were able to demonstrate that **7d** was also obtained as the (*S*)-isomer by conversion of this product into (2*S*,5*S*)-5-butyl-2-(*tert*-butoxycarbonyl)pyrrolidine and by comparison of the sign of rotation with that previously reported for this material.[17] Product **7f** was also shown to be the (*S*)-isomer by comparison of the sign of rotation

Table 4
Enantioselective addition of glycine imine **2** to various Michael acceptors[13,14]



Entry	EWG	Time (h)	Yield (%)[a]	ee[b] (%)
a	CO_2Me	8	95	98 (−) (*S*)
b	COMe	2.5	80	95 (−) (*S*)
c	COEt	6	87	95 (−)
d	CO*n*-Bu	5	65	91 (−) (*S*)
e	COPh	1.5	63	91[15] (−)
		2.5[c]	99	89[15] (−)
f	CN	5	58	95 (−) (*S*)
		8[c]	77	96 (−) (*S*)
g	SO_2Ph	1.5	90	92 (−)
h	$P(O)(OEt)_2$	10	<10	—
i	$CONMe_2$	10	<10	—

[a] Determined by ^{1}H NMR.
[b] Determined by HPLC.
[c] Slow addition of Michael acceptor.

with previously reported data[4g] and **7b** by comparison of HPLC retention times with previously published data.[6c] As yet, we have not been able to unambiguously establish the absolute stereochemistry of Michael adducts **7c, 7e and 7g** and so the signs of rotation are given in Table 4. It should be noted that PTC **1** also gives (*S*)-selectivity in the corresponding alkylation reactions (Table 1) and so the Michael additions may be proceeding via similar ion-pair intermediates to those proposed previously for the corresponding alkylation reactions.[1]

In conclusion, we have shown that use of a co-catalyst can greatly enhance the effectiveness of KOH-mediated asymmetric PTC Michael additions involving glycine imine **2**. The enantioselectivities obtained using this method generally exceed those previously reported for the same substrates using alternative cinchona alkaloid PTC procedures.[4g,h,5] We are currently investigating the application of this chemistry in target synthesis.

Acknowledgements

Financial support for this work was provided by EPSRC and GlaxoSmithKline.

References and notes

1. For reviews covering recent developments in asymmetric phase-transfer catalysis see: (a) Maruoka, K. *Org. Proc. Res. Dev.* **2008**, *12*, 679; (b) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656; (c) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222; (d) Vachon, J.; Lacour, J. *Chimia* **2006**, *60*, 266; (e) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506; (f) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518; (g) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013.
2. For a review of glycine imine chemistry see: O'Donnell, M. J. *Aldrichim. Acta.* **2001**, *34*, 3.
3. For examples of application in target synthesis see: (a) Wang, Y.-G.; Ueda, M.; Wang, X.; Han, Z.; Maruoka, K. *Tetrahedron* **2007**, *63*, 6042; (b) Lee, J.-H.; Jeong, B.-S.; Ku, J.-M.; Jew, S.-S.; Park, H.-G. *J. Org. Chem.* **2006**, *71*, 6690; (c) Lygo, B.; Slack, D.; Wilson, C. *Tetrahedron Lett.* **2005**, *46*, 6629; (d) Fukuta, Y.; Ohshima, T.; Gnanadesikan, V.; Shibuguchi, T.; Nemoto, T.; Kisugi, T.; Okino, T.; Shibasaki, M. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5433; (e) Lygo, B.; Humphreys, L. D. *Synlett* **2004**, 2809; (f) Kim, S.; Lee, J.; Lee, T.; Park, H.-G.; Kim, D. *Org. Lett.* **2003**, *5*, 2703; (g) Armstrong, A.; Scutt, J. N. *Org. Lett.* **2003**, *5*, 2331; (h) Lygo, B.; Andrews, B. I. *Tetrahedron Lett.* **2003**, *44*, 4499; (i) Boeckman, R. K., Jr.; Clark, T. J.; Shook, B. C. *Org. Lett.* **2002**, *4*, 2109.
4. For examples of highly enantioselective PTC Michael additions involving glycine imines see: (a) Elsner, P.; Bernardi, L.; Salla, G. D.; Overgaard, J.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 4897; (b) Bernardi, L.; Lopez-Cantarero, J.; Niess, B.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 5772; (c) Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Ohshima, T.; Shibasaki, M. *Chem. Asian J.* **2007**, *2*, 794; (d) Arai, S.; Takahashi, F.; Tsuji, R.; Nishida, A. *Heterocycles* **2006**, *67*, 495; (e) Lygo, B.; Allbutt, B.; Kirton, E. H. M. *Tetrahedron Lett.* **2005**, *46*, 4461; (f) Akiyama, T.; Hara, M.; Fuchibe, K.; Sakamoto, S.; Yamaguchi, K. *Chem. Commun.* **2003**, 1734; (g) Corey, E. J.; Zhang, F-Y. *Org. Lett.* **2000**, *2*, 1097; (h) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347.
5. For highly enantioselective Michael additions of imine **2** mediated by cinchona alkaloid-derived quaternary ammonium salts in conjunction with phosphazine bases see: O'Donnell, M. J.; Delgado, F.; Dominguez, E.; de Blas, J.; Scott, W. L. *Tetrahedron: Asymmetry* **2001**, *12*, 821.
6. For other examples of highly enantioselective Michael additions of glycine imines see: (a) Tsubogo, T.; Saito, S.; Seki, K.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 13321; (b) Ryoda, A.; Yajima, N.; Haga, T.; Kumamoto, T.; Nakanishi, W.; Kawahata, M.; Yamaguchi, K.; Ishikawa, T. *J. Org. Chem.* **2008**, *73*, 133; (c) Ishikawa, T.; Araki, Y.; Kumamoto, T.; Seki, H.; Fukuda, K.; Isobe, T. *Chem. Commun.* **2001**, 245.
7. (a) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595; (b) Lygo, B.; Crosby, J.; Lowdon, T. R.; Peterson, J. A.; Wainwright, P. G. *Tetrahedron* **2001**, *57*, 2403.
8. For an example of the use of a cinchona alkaloid-derived quaternary ammonium phenoxide as a catalyst for homogeneous Michael additions involving silylketene acetals see: Tozawa, T.; Yamane, Y.; Mukaiyama, T. *Chem. Lett.* **2006**, *35*, 56.
9. Reagent grade KOH pellets were purchased from Fisher Scientific, UK and used as supplied.
10. For an example of crown ethers as co-catalysts for PTC asymmetric alkylations see: Shirakawa, S.; Yamamoto, K.; Kitamura, M.; Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 625.
11. For an example of mesitol as a co-catalyst for PTC eliminations see: Makoswa, M.; Chesnokov, A. *Tetrahedron* **2000**, *56*, 3553.
12. (a) Lygo, B.; Gardiner, S.; McLeod, M. C.; To, D. C. M. *Org. Biomol. Chem.* **2007**, *5*, 2283; (b) Lygo, B.; To, D. C. M. *Tetrahedron Lett.* **2001**, *42*, 1343.
13. *Representative procedure*: Potassium hydroxide (19 mg, 0.34 mmol) was added to a solution of PTC **1** (10.5 mg, 10 mol %) and mesitol (2.3 mg, 10 mol %) in dichloromethane (1 mL) at 0 °C and the mixture was stirred for 30 min. During this time a colour change from yellow to orange/brown was observed. The mixture was then cooled to −78 °C and a solution of glycine imine **2** (50 mg, 0.17 mmol) in dichloromethane (1 mL) was added, followed by methyl acrylate (23 μL, 0.26 mmol). The reaction mixture was stirred at −78 °C until complete by TLC (8 h), and then immediately filtered through a plug of magnesium sulfate. After warming to room temperature the solution was concentrated under reduced pressure to afford the crude product **7a**. Yields were calculated by ^{1}H NMR using veratrole as an internal standard. An aliquot of the crude product was purified by flash column chromatography on silica gel (90:9:1, petroleum ether/EtOAc/Et_3N) to give **7a** as a colourless oil, R_f 0.25 (9:1 petroleum ether/EtOAc); $[\alpha]_D$ −96.0 (98% ee, *c* 0.7 in $CHCl_3$); ν_{max} (film)/cm^{-1} 2977, 1736, 1623, 1445, 1368, 1152; ^{1}H NMR (400 MHz, $CDCl_3$)[4h] 7.66–7.64 (2H, m, ArH), 7.46–7.31 (6H, m, ArH), 7.20–7.18 (2H, m, ArH), 3.98 (1H, dd, *J* 7.0, 5.5, $CHCO_2$), 3.60 (3H, s, OCH_3), 2.41–2.37 (2H, m, CH_2), 2.26–2.20 (2H, m, CH_2), 1.45 (9H, s, $(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 173.6 (C), 170.8 (C), 139.5 (C), 136.5 (C), 130.3 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.0 (CH), 127.8 (CH), 81.2 (C), 64.8 (CH), 51.5 (CH_3), 30.5 (CH_2), 28.7 (CH_2), 28.0 (CH_3); *m/z* (ESI+) found $[M+H]^+$ 382.1996; $C_{23}H_{27}NO_4$ requires 382.2013. R_t HPLC (Chiralcel OD–H column, 97.5:2.5 hexane/*iso*-propyl alcohol, 0.5 mL/min, 254 nm) 12.9 min (*R*)-isomer, 15.8 min (*S*)-isomer.
14. *Analytical data for previously unreported compounds*: Compound **7d**. Pale yellow oil, R_f 0.45 (9:1 petroleum ether/EtOAc); $[\alpha]_D$ −53.4 (91% ee, *c* 0.7 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3006, 2962, 2934, 2874, 1726, 1153; ^{1}H NMR (400 MHz, $CDCl_3$) 7.63 (2H, d, *J* 9.0, ArH), 7.48–7.42 (3H, m, ArH), 7.36–7.31 (3H, m, ArH), 7.18–7.15 (2H, m, ArH), 3.95 (1H, app t, *J* 6.0, $CHCO_2$), 2.59–2.47 (2H, m, CH_2), 2.41 (2H, app t, *J* 7.5, $COCH_2$), 2.21–2.15 (2H, m, CH_2), 1.58–1.50 (2H, m, CH_2), 1.44 (9H, s, $(CH_3)_3$) 1.35–1.25 (2H, m, CH_2), 0.88 (3H, t, *J* 7.0, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) 210.7 (C), 171.1 (C), 170.4 (C), 139.5 (C), 136.5 (C), 130.3 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.0 (CH), 127.7 (CH), 81.1 (C), 64.8 (CH), 42.6 (CH_2), 38.9 (CH_2), 28.1 (CH_2), 27.8 (CH_2), 25.9 (CH_2), 22.4 (CH_2), 13.9 (CH_3); *m/z* (ESI+) found $[M+H]^+$ 408.2518; $C_{26}H_{34}NO_3$ requires 408.2460. R_t HPLC (Chiralcel OD–H column, 99:1 hexane/ethanol, 0.5 mL/min, 254 nm) 12.3 min (*R*)-isomer, 14.9 min (*S*)-isomer.
Compound **7e**. Pale yellow oil, R_f 0.2 (9:1 petroleum ether/EtOAc); $[\alpha]_D$ −15.6 (91% ee, *c* 0.7 in $CHCl_3$); ν_{max} (film)/cm^{-1} 3059, 2976, 2933, 1731, 1685, 1150; ^{1}H NMR (400 MHz, $CDCl_3$) 7.97–7.94 (2H, m, ArH), 7.67–7.64 (2H, m, ArH), 7.58–7.53 (1H, m, ArH), 7.48–7.30 (8H, m, ArH), 7.17–7.13 (2H, m, ArH), 4.08 (1H, dd, *J* 6.5, 5.5, $CHCO_2$), 3.18–2.99 (2H, m, CH_2), 2.36–2.22 (2H, m, CH_2), 1.46 (9H, s, $(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 199.7 (C), 171.1 (C), 170.6 (C), 139.5 (C), 136.9 (C), 136.5 (C), 132.9 (CH), 130.3 (CH), 128.8 (CH), 128.6 (CH), 128.6 (CH), 128.5 (CH), 128.1 (CH), 128.0 (CH), 127.7 (CH), 81.2 (C), 64.8 (CH), 34.7 (CH_2), 28.2 (CH_2), 28.1 (CH_3); *m/z* (ESI+) found $[M+H]^+$ 428.2207; $C_{29}H_{30}NO_3$ requires 428.2220.
15. The enantiomeric excess of **7e** was determined by conversion to 2-*tert*-butoxycarbonyl-5-phenyl-3,4-dihydro-2*H*-pyrrole, followed by HPLC analysis: the crude imine **7e** was hydrolyzed by addition of a solution of 15% aqueous citric acid (1 mL) and tetrahydrofuran (2 mL). The resulting solution was stirred at rt for 2 h then diluted with dichloromethane (2 mL). The organic layer was washed with brine (3 × 3 mL), dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (9:1 petroleum ether/EtOAc) to afford 2-*tert*-butoxycarbonyl-5-phenyl-3,4-dihydro-2*H*-pyrrole (69% overall from **2**) as a colourless oil, R_f 0.2 (9:1 petroleum ether/EtOAc); $[\alpha]_D$ +88.0 (91% ee, *c* 0.7 in $CHCl_3$); ν_{max} (film)/cm^{-1} 2978, 1732, 1154; ^{1}H NMR (400 MHz, $CDCl_3$) 7.90–7.88 (2H, m, ArH), 7.47–7.38 (3H, m, ArH), 4.84–4.80 (1H, m, H-2), 3.17–3.08 (1H, m, H-4_a), 3.02–2.95 (1H, m, H-4_b), 2.37–2.28 (1H, m, H-3_a), 2.21–2.12 (1H, m, H-3_b), 1.50 (9H, s, $(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) 175.8 (C), 172.3 (C), 134.1 (C), 130.8 (CH), 128.5 (CH), 128.1 (CH), 81.1 (C), 75.4 (CH), 35.4 (CH_2), 28.1 (CH_3), 26.8 (CH_2); *m/z* (ESI+) found $[M+H]^+$ 246.1487; $C_{15}H_{19}NO_2$ requires 246.1489. R_t HPLC (Chiralcel OD–H column, 90:10 hexane/*iso*-propyl alcohol, 0.5 mL/min; 254 nm) 11.3 min (major), 19.8 min (minor).
16. Besson, M.; Delbecq, F.; Gallezot, P.; Neto, S.; Pinel, C. *Chem. Eur. J.* **2000**, *6*, 949.
17. Ibrahim, H. H.; Lubell, W. D. *J. Org. Chem.* **1993**, *58*, 6438.