A site isolation-enabled organocatalytic approach to enantiopure γ-amino alcohol drugs

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ABSTRACT

Solid support-enabled site isolation has previously allowed to use paraldehyde as an acetaldehyde surrrogate in aldol reactions. However, only electron-poor aldehydes were tolerated by the system. Herein, we show that the temporary conversion of benzaldehyde into η^6-benzaldehyde $Cr(CO)_3$ circumvents this limitation. Asymmetric synthesis of (R)-Phenoperidine, as well as formal syntheses of (R)-Fluoxetine and (R)-Atomoxetine, illustrate the benefits of this strategy.

1. Introduction

The direct cross-aldol reaction represents one of the most important carbon-carbon bond forming processes since it can provide an efficient approach to both naturally occurring and synthetically important building blocks.[1-5] During the past decade, a variety of enamine-mediated aminocatalytic processes have been developed and successfully applied in asymmetric cross-aldol reaction.[6-9] However, most of these examples are not efficient with acetaldehyde as the donor due to its high reactivity unavoidably leading to a variety of by-products arising from its oligomerization and self-aldolization.[10-11] Ten years ago, the Hayashi group reported the first organocatalytic direct cross-aldol reaction of acetaldehyde with aromatic aldehydes using a diarylprolinol as the catalyst.[12] Later, the use in the same reactions of chiral primary amine catalysts under neat conditions[13] and of suitably modified diarylprolinol catalysts in aqueous media,[14] have also been reported. More recently, we have disclosed a highly enantioselective version of the reaction promoted by a dual catalytic system (polystyrene-bound sulfonic acid **1** and polystyrene-supported diarylprolinol catalyst **2**, Figure 1), which enabled the use of paraldehyde as a convenient source of acetaldehyde.[15] Compared to acetaldehyde, paraldehyde is less expensive, easier to handle (b.p. 123 °C) and can be deoligomerized in situ by polystyrene-bound sulfonic acid **1**. The site isolation scenario generated under these conditions[16-19] enabled catalyst **1** to work compatibly with **2** in one pot in a highly recyclable manner, furnishing the aldol products in good yields and excellent enantioselectivities. This methodology granted access to enantioenriched 1-arylpropane-1,3-diols, a privileged core structure occurring in a variety of drugs and natural products.[20]

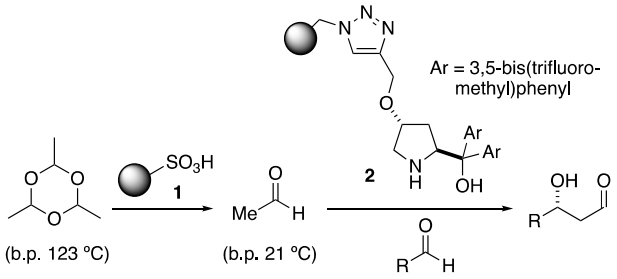
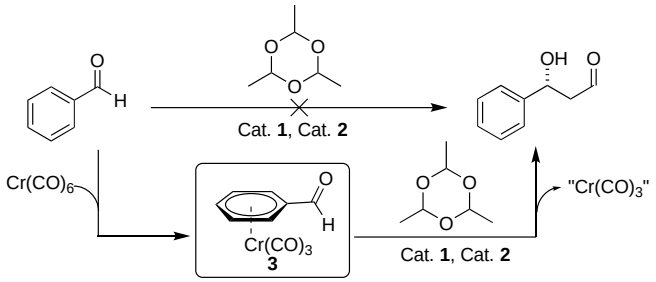


Figure 1. Cascade deoligomerization and cross-aldol reaction mediated by **1**/**2** operating under site isolation.

However, the drawback of this method was the fact that only electron-poor benzaldehydes could be used as effective substrates (Scheme 1, top). Considering the importance of 3-phenyl-3-hydroxypropanal as a key building block in the synthesis of many active pharmaceutical ingredients, we analyzed methods allowing the reversible electronic modification of benzaldehyde that could favor its participation in the cross-aldol reaction.

It is known that the formation of η^6-arene-$Cr(CO)_3$ complexes importantly decreases the electron density of the parent arene and modifies accordingly its reactivity.[21-22] From a practical perspective, these complexes are easily formed upon reaction of $Cr(CO)_6$ with aromatic substrates, and the metal moiety can be later removed in quantitative yield by exposure to visible light.[23-24] Thus, the complexation/decomplexation process has normally low impact on the efficiency of the overall process. In 2011, Walsh *et al.* exploited this approach to favour the generation of nucleophiles for allylic substitution reaction,[25-26] and the same strategy has been recently applied by Larrosa *et al.* for enhancing the reactivity of C-H bonds in arylation reactions.[27] With these precedents in mind, we assumed that the η^6-benzaldehyde complex **3** could be used as an activated benzaldehyde surrogate

in the cross-aldol reaction with paraldehyde mediated by the **1**/**2** dual catalytic system (Scheme 1, bottom).

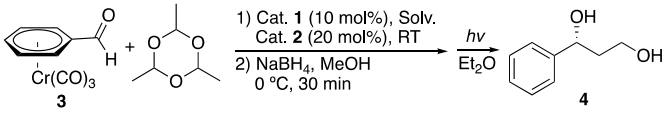


Scheme 1. Deoligomerization/cross-aldol reaction of paraldehyde with complex **3** mediated by the **1**/**2** dual catalytic system.

2. Results and discussion

Initially, we investigated the cross-aldol reaction of the tricarbonyl (η^6-benzaldehyde) chromium (0) with paraldehyde mediated by the dual catalytic system **1**/**2** in DMF (Table 1, entry 1) but the target aldol product was not formed at all in this solvent. A subsequent solvent screening showed that when acetonitrile was employed the product can be isolated in 18% yield and 93% ee (entry 3).

Table 1. Tandem deoligomerization plus asymmetric cross-aldol reaction of tricarbonyl (η^6-benzaldehyde) chromium (0) with paraldehyde catalyzed by **1**/**2**.[a]



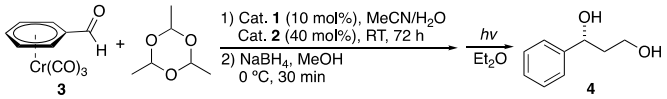
Entry	Time (h)	Solvent	Paraldehyde (equiv.)	Yield (%)[b]	ee (%)[c]
1	24	DMF	2	0	–
2	24	CH_3NO_2	2	15	92
3	24	MeCN	2	18	93
4[d]	24	MeCN	2	12	92
5[e]	24	MeCN	2	17	93
6	24	MeCN/H_2O	2	20	93
7[f]	24	MeCN/H_2O	2	17	93
8[g]	24	MeCN/H_2O	2	19	93
9	72	MeCN/H_2O	2	38	93
10	72	MeCN/H_2O	5	41	93
11	72	MeCN/H_2O	10	33	93
12	72	MeCN/H_2O	20	30	92
13	72	Paradehyde	–	20	92
14[h]	72	MeCN/H_2O	5	49	93
15[i]	**72**	**MeCN/H_2O**	**5**	**61**	**93**

[a]The reaction was carried out with **3** (0.1 mmol), paraldehyde, **1** (10 mol%), **2** (20 mol%) and H_2O (0.5 mmol) in 0.3 mL solvent. [b]Determined by ^1H NMR using mesitylene as internal standard. [c]By HPLC. [d]0.01 mmol $PhCO_2H$ added. [e]0.01 mmol *p*-$NO_2C_6H_4CO_2H$ added. [f]At 40 °C. [g]Using microwave at 40 °C. [h]30 mol% of **2** was used. [i]40 mol% of **2** was used.

A screening of additives including benzoic acid, *p*-nitrobenzoic acid and water revealed the latter as the most convenient one (entries 4-6). When raising the temperature, either with conventional heating or using the microwave, the enantioselectivity was maintained but the yield slightly decreased (entries 7 and 8). In order to evaluate the effect of different reaction times on the yield and enantioselectivity, we carried out a series of comparative experiments[§] which showed that after 72 hours the reduced aldol product **4** could be obtained in 38% yield and 93% ee (entry 9). Subsequently, the use of different amounts of paraldehyde was examined (entries 10-12). The improvement was not significant, but 5 equiv. seemed to be a bit better. Finally, increasing the loading of polystyrene-supported catalyst **2** led to a major yield improvement (up to 61%) when 40 mol% of this catalyst was used (entry 15).

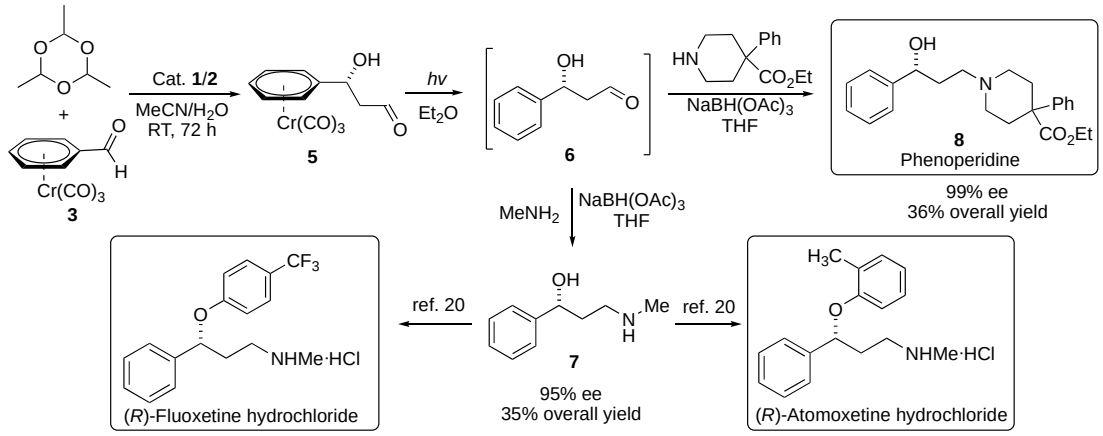
It is to be noted that such a high catalyst loading can only be justified if the dual catalytic system is amenable to recycling.[28-30] In this regard, it is worth mentioning that the recovery of the two different polystyrene-supported catalysts can be achieved by simple filtration without separating the two resins. Gratifyingly, the mixture of the two catalysts can be reactivated by briefly washing with AcOH after each reaction cycle. The role of the acid is presumably to hydrolyse the parasite oxazolidine formed by catalyst **2** and acetaldehyde, thus increasing the effective amount of catalytic species.[15] Using this strategy, the **1**/**2** dual catalytic system could be reused for five cycles with essentially the same results. On the sixth cycle, the aldol product was still obtained in high enantioselectivity (90% ee), albeit with slightly decreased yield (Table 2).

Table 2. Recycling in the tandem deoligomerization/ asymmetric cross-aldol reaction of tricarbonyl (η^6-benzaldehyde) chromium (0) with paraldehyde catalyzed by **1**/**2**.



Run	Yield (%)	ee (%)
1	58	93
2	60	93
3	54	92
4	53	93
5	50	92
6	38	90

As already mentioned, enantiomerically enriched 1,3-diols and β-hydroxyaldehydes are versatile building blocks for the synthesis of a wide variety of natural products and commercially important drugs.[31-33] For instance, enantioenriched diol **4** is a key intermediate in the preparation of the selective serotonin reuptake inhibitor (*R*)-fluoxetine (Prozac®) and the norepinephrine reuptake inhibitor (*R*)- atomoxetine (Strattera®), which are important drugs for the treatment of important psychiatric disorders.[20, 34]



Scheme 2 Synthesis of drugs and intermediates with the present methodology.

According to previous literature procedures, the reduced cross-aldol product **4** can be converted into amino alcohol **7**, a common precursor to both drugs, in four steps and 36% overall yield.[20] We have now found (Scheme 2) that crude aldol **6**, obtained by decomplexation of **5** in ether solution on exposure to visible light, can be converted into **7** (95% ee) in a single step by reductive amination with $MeNH_2$ (35% overall yield). The possibility of applying a reductive amination greatly facilitates the introduction of an amine moiety in this position. Phenoperidine **8**,[35-37] another well-known drug can also be synthesized in a single step from crude **6** upon treatment with ethyl 4-phenylpiperidine-4-carboxylate and $NaBH(OAc)_3$ in 36% overall yield and 99% ee.

3. Conclusions

In conclusion, we have developed an efficient approach for enhancing the reactivity of benzaldehyde in the cross-aldol reaction with acetaldehyde resulting from the deoligomerization of paraldehyde. The tandem process is mediated by the dual polymer-supported catalytic system **1/2**, which operates under site isolation conditions in a recyclable manner. The strategy reported herein, involving η^6-coordination to $Cr(CO)_3$, has been applied to overcome the challenges and limitation of cross-aldol reaction of acetaldehyde with benzaldehyde, affording 1-phenylpropane-1,3-diol in high yield and excellent enantioselectivity. The crude, enantioenriched aldol **6** has been applied to the development of very short formal syntheses of the important drugs (*R*)-Fluoxetine and (*R*)-Atomoxetine.

4. Experimental

4.1. Procedure for the cross-aldol reaction and decomplexation[28]

Catalyst **1** (10 mol%, 0.02 mmol, 6.7 mg), catalyst **2** (40 mol%, 0.08 mmol, 170.4 mg) and tricarbonyl (η^6-benzaldehyde) chromium (0) (0.2 mmol, 51.4 mg) were mixed in a brown vial with acetonitrile (0.6 mL). Then paraldehyde (137 µL, 5.0 eq., 1.0 mmol) and deionized water (1.8 µL, 0.1 mmol) were added and the brown vial was sealed and shaken at room temperature for 72 hours. After that the reaction mixture was filtered and washed with methanol (3 × 0.8 mL). The filtrates were combined and cooled to 0 ºC, then $NaBH_4$ (37.8 mg, 1.0 mmol) was added and the mixture was stirred for 20 minutes. After that, the reaction was quenched with aqueous NH_4Cl (2 mL) and extracted with ethyl acetate (3 × 5 mL). The organic layer was then washed with brine (2 mL), dried with anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O (5 mL) and this solution was exposed to air and light until a colorless solution with a green or brown precipitate resulted. Filtration through celite, concentration and purification of the crude product by column chromatography on silica gel (hexane/ethyl acetate 1:1), provided the pure product **4**[12] (0.11 mmol, 18 mg) as a colorless oil in 58% yield and 93% ee.

(*R*)-1-phenylpropane-1,3-diol (4). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.85-2.04 (m, 2H), 2.88 (brs, 1H), 3.34 (brs, 1H), 3.81 (t, *J* = 5.4 Hz, 2H), 4.92 (dd, *J* = 3.9, 8.4 Hz, 1H), 7.23-7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.5, 61.5, 74.4, 125.6 (×2), 127.6, 128.5 (×2), 144.3; HPLC (Chiralcel AD-H, Hexane/*i*-propanol (97:3), flow rate = 1.0 mL min^{-1}, λ = 210 nm): t_{major} = 35.0 min, t_{minor} = 37.2 min.

4.2. General procedure for catalyst recycling

Catalyst **1** (10 mol%, 0.02 mmol, 6.7 mg), catalyst **2** (40 mol%, 0.08 mmol, 170.4 mg) and tricarbonyl (η^6-benzaldehyde) chromium (0) (0.2 mmol, 51.4 mg) were mixed in a brown vial with acetonitrile (0.6 mL). Then paraldehyde (137 µL, 5.0 eq., 1.0 mmol) and deionized water (1.8 µL, 0.1 mmol) were added and the brown vial was sealed and shaken at room temperature. After 72 h, the mixture was filtered and washed with acetonitrile (3 × 1 mL), the filtrate being treated as described above to isolate the desired compound. As for the mixed catalysts recovered, they were washed with acetic acid (0.5 mL) and acetonitrile (4 × 1 mL), repeating this procedure several times until the solvent was colorless. After that, the mixed catalysts were dried at 40 ºC under vacuum for 6 h and then used in the next reaction.

4.3. Synthesis and characterization of 7 and 8[15]

Catalyst **2** (40 mol%, 0.12 mmol, 255.6 mg), catalyst **1** (10 mol%, 0.03 mmol, 10.1 mg) and the tricarbonyl (η^6-benzaldehyde) chromium (0) (0.3 mmol, 77 mg) were mixed in a brown vial with acetonitrile (0.9 mL). Then, paraldehyde (5.0 eq., 206 µL, 1.5 mmol) and deionized water (2.7 µL, 0.15 mmol) were added and the brown vial was sealed and shaken at room temperature for 72 hours. After that, the reaction mixture was filtered and washed with acetonitrile (3 × 1.2 mL) and AcOH (15% in THF, 3 × 1.2 mL). The filtrates were combined and crude product **5** was obtained after removal of the solvent under vacuum. Then, this was dissolved in Et_2O (25 mL) and the resulting solution was exposed to air and light until a colorless solution with a green or brown precipitate resulted. Filtration through celite and concentration gave the crude product **6**.

Crude product **6** was dissolved in anhydrous THF (3 mL) and methylamine (33 wt% in EtOH, 1.5 mmol, 140 mg) and

anhydrous Na_2SO_4 (2.1 mmol, 0.3 g) were added. The mixture was stirred for 5 hours and then $NaBH(OAc)_3$ (2.0 eq., 0.6 mmol, 127 mg) was added in portions. After stirring overnight, the solution was quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 8 mL). The organic layer was washed with brine (2 mL) and dried with anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave the crude mixture, which was purified by fast column chromatography on silica gel, with CH_2Cl_2/MeOH/ NH_4OH mixtures as eluent. In this manner, 20 mg of **7** (0.12 mmol, 35% overall yield for three steps) were obtained as a colorless oil with 95% ee (determined by chiral HPLC analysis of their *N*-acetyl derivative according to a reported procedure[34]; see ESI).

(*R*)-3-(Methylamino)-1-phenylpropan-1-ol (7). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 1.72-1.96 (m, 2H), 2.45 (s, 3H), 2.81-2.95 (m, 2H), 4.03 (brs, 2H), 4.93 (dd, *J* = 3.1, 8.7 Hz, 1H), 7.21-7.39 (m, 5H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 36.0, 36.8, 50.4, 75.5, 125.6 (×2), 126.9, 128.2 (×2), 145.1. **$[\alpha]_D^{25}$** = +45.8 (*c* = 0.1, $CHCl_3$). It is a known compound.[20]

The crude **6** (see above) was dissolved in anhydrous THF (3 mL) and ethyl 4-phenylpiperidine-4-carboxylate (2.0 eq., 0.6 mmol, 140 mg) and anhydrous Na_2SO_4 (2.1 mmol, 0.3 g) were added. The mixture was stirred for 5 hours and then $NaBH(OAc)_3$ (2.0 eq., 0.6 mmol, 127 mg) was added in portions. After stirring overnight, the solution was quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 8 mL). The organic layer was washed with brine (2 mL) and dried with anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave a residue which was purified by fast column chromatography on silica gel, with CH_2Cl_2/MeOH/ NH_4OH mixtures as eluent. In this manner, 40 mg of **8** (0.11 mmol, 36% overall yield for three steps) were obtained as a yellow oil with 99% ee (determined by chiral HPLC).

Phenoperidine (8). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 1.17 (t, *J* = 7.1 Hz, 3H), 1.47-1.53 (m, 1H), 1.67-1.73 (m, 1H), 1.80-1.88 (m, 1H), 1.97-2.08 (m, 2H), 2.34 (t, *J* = 11.7 Hz, 1H), 2.55-2.67 (m, 4H), 2.87-2.88 (m, 1H), 3.10-3.13 (m, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.97 (dd, *J* = 2.7, 9.9 Hz, 1H), 7.20 - 7.40 (m, 10H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 14.1, 31.7, 33.5, 34.1, 46.4, 49.0, 50.5, 57.6, 61.0, 74.7, 125.7 (×2), 127.1 (×2), 127.2 (×2), 128.3 (×2), 128.6, 128.6 (×2), 144.9, 174.1. **HPLC** (Chiralcel IA, Hexane/*i*-propanol (90:10), flow rate = 1.0 mL min^{-1}, λ = 215 nm): t_{major} = 20.4 min, t_{minor} = 17.0 min. **HRMS** calcd for $C_{23}H_{29}NO_3$ $(M + H)^+$: 368.2220, found: 368.2213. **$[\alpha]_D^{25}$** = +21.5 (*c* = 0.1, $CHCl_3$). **IR** (ATR): ν = 539, 698, 761, 858, 1022, 1106, 1177, 1214, 1447, 1496, 1601, 1721, 2586, 2937 cm^{-1}.

Dedication

This paper is warmly dedicated to Professor Léon Ghosez, to honor its fruitful and long lasting compromise with the progress of chemical science

Acknowledgments

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Appendix A. Supplementary Data

References and notes

1. Mahrwald, R. *Chem. Rev.* **1999,** *99*, 1095-1120.
2. Machajewski, T. D.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2000,** *39*, 1352-1375.
3. Palomo, C.; Oiarbide, M.; Garcia, J. M. *Chem. Soc. Rev.* **2004,** *33*, 65-75.
4. Trost, B. M.; Brindle, C. S. *Chem. Soc. Rev.* **2010,** *39*, 1600-1632.
5. Machajewski, T. D.; Wong, C.-H. *Angew. Chem.* **2000,** *112*, 1406-1430.
6. Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007,** *107*, 5471-5569.
7. Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004,** *43*, 5138-5175.
8. Alcaide, B.; Almendros, P. *Angew. Chem. Int. Ed.* **2003,** *42*, 858-860.
9. List, B. *Acc. Chem. Res.* **2004,** *37*, 548-557.
10. Alcaide, B.; Almendros, P. *Angew. Chem. Int. Ed.* **2008,** *47*, 4632-4634.
11. Hayashi, Y.; Samanta, S.; Itoh, T.; Ishikawa, H. *Org. Lett.* **2008,** *10*, 5581-5583.
12. Hayashi, Y.; Itoh, T.; Aratake, S.; Ishikawa, H. *Angew. Chem. Int. Ed.* **2008,** *47*, 2082-2084.
13. Hu, S.; Zhang, L.; Li, J.; Luo, S.; Cheng, J.-P. *Eur. J. Org. Chem.* **2011,** *2011*, 3347-3352.
14. Qiao, Y.; Chen, Q.; Lin, S.; Ni, B.; Headley, A. D. *J. Org. Chem.* **2013,** *78*, 2693-2697.
15. Fan, X.; Rodríguez-Escrich, C.; Wang, S.; Sayalero, S.; Pericàs, M. A. *Chem. Eur. J.* **2014,** *20*, 13089-13093.
16. Fan, X.; Rodríguez-Escrich, C.; Sayalero, S.; Pericàs, M. A. *Chem. Eur. J.* **2013,** *19*, 10814-10817.
17. Hecht, S.; Fréchet, J. M. J. *Angew. Chem. Int. Ed.* **2001,** *40*, 74-91.
18. Helms, B.; Guillaudeu, S. J.; Xie, Y.; McMurdo, M.; Hawker, C. J.; Fréchet, J. M. J. *Angew. Chem. Int. Ed.* **2005,** *44*, 6384-6387.
19. Chi, Y.; Scroggins, S. T.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2008,** *130*, 6322-6323.
20. Gao, Y.; Sharpless, K. B. *J. Org. Chem.* **1988,** *53*, 4081-4084.
21. Davies, S. G.; Donohoe, T. J. *Synlett* **1993,** *1993*, 323-332.
22. Solladié-Cavallo, A. *Polyhedron* **1985,** *4*, 901-927.
23. Mandal, S. K.; Sarkar, A. *J. Org. Chem.* **1998,** *63*, 1901-1905.
24. Uemura, M.; Nishikawa, N.; Take, K.; Ohnishi, M.; Hirotsu, K.; Higuchi, T.; Hayashi, Y. *J. Org. Chem.* **1983,** *48*, 2349-2356.
25. Zhang, J.; Stanciu, C.; Wang, B.; Hussain, M. M.; Da, C.-S.; Carroll, P. J.; Dreher, S. D.; Walsh, P. J. *J. Am. Chem. Soc.* **2011,** *133*, 20552-20560.
26. McGrew, G. I.; Temaismithi, J.; Carroll, P. J.; Walsh, P. J. *Angew. Chem. Int. Ed.* **2010,** *49*, 5541-5544.
27. Ricci, P.; Krämer, K.; Cambeiro, X. C.; Larrosa, I. *J. Am. Chem. Soc.* **2013,** *135*, 13258-13261.
28. Fan, X.; Sayalero, S.; Pericàs, M. A. *Adv. Synth. Catal.* **2012,** *354*, 2971-2976.
29. Alza, E.; Sayalero, S.; Kasaplar, P.; Almaşi, D.; Pericàs , M. A. *Chem. Eur. J.* **2011,** *17*, 11585-11595.
30. Riente, P.; Mendoza, C.; Pericas, M. A. *J. Mater. Chem.* **2011,** *21*, 7350-7355.
31. De Castro, K. A.; Ko, J.; Park, D.; Park, S.; Rhee, H. *Org. Process Res. Dev.* **2007,** *11*, 918-921.
32. Sabitha, G.; Padmaja, P.; Yadav, J. S. *Helv. Chim. Acta* **2008,** *91*, 2235-2239.
33. Sasikumar, M.; Nikalje, M. D. *Synth. Commun.* **2012,** *42*, 3061-3067.
34. Liu, D.; Gao, W.; Wang, C.; Zhang, X. *Angew. Chem. Int. Ed.* **2005,** *44*, 1687-1689.
35. Duc, C. L.; Charlon, C.; Delord, C. A.; Cros, J.; Monsarrat, B. *J. Labelled Compd. Radiopharm.* **1978,** *15*, 693-696.
36. Fischler, M.; Levron, J. C.; Trang, H.; Brodaty, D.; Dubois, C.; Guilmet, D.; Vourc'h, G. *Br. J. Anaesth.* **1985,** *57*, 877-882.
37. Fischler, M.; Levron, J. C.; Trang, H.; Vaxelaire, J. F.; Flaisler, B.; Vourc'H, G. *Br. J. Anaesth.* **1985,** *57*, 872-876.