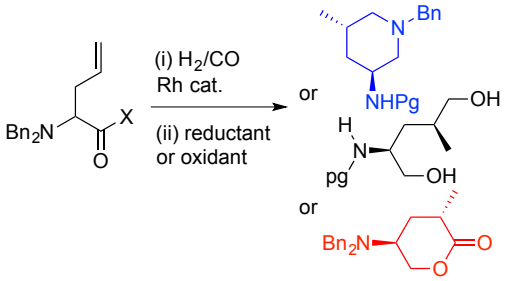
Diastereoselective and branched-aldehyde-selective tandem hydroformylation-hemiaminal formation: synthesis of functionalized piperidines and amino-alcohols.

Rachael Pittaway, José A. Fuentes and Matthew L. Clarke*

School of Chemistry, Purdie Building, North Haugh, St Andrews, Fife, KY16 9ST, Scotland, United Kingdom



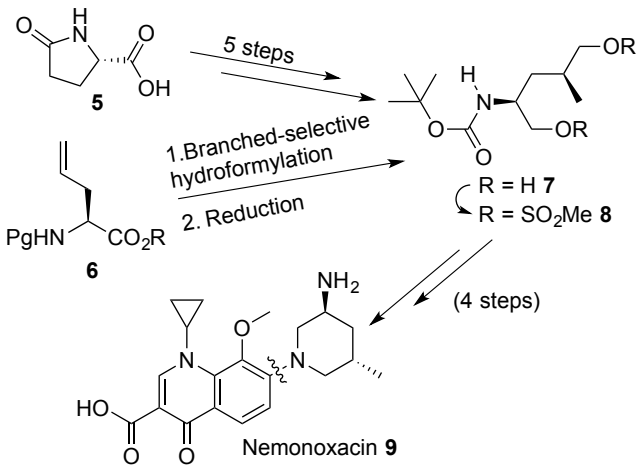
Abstract: Starting from readily available allylglycine, a tandem hydroformylation-hemiaminal formation reaction has been developed for the synthesis of chiral functionalized piperidines, with very good diastereoselectivity and branched regioselectivity using Rh/(*S,S,S*)-BOBPHOS catalysts. Tandem hydroformylation-hemiacetal formation also proceeds with good diastereoselectivity (88:12), with the hemiacetal product being hydrogenated with retention of stereochemistry, to give a chiral intermediate used in the synthesis of the new antibiotic, Nemonoxacin.

Hydroformylation of terminal alkenes generally favours the linear aldehyde; sometimes with excellent selectivity.[1] Linear-selective hydroformylation is quite a robust reaction at large scale, but also as synthetic methodology for the synthesis of complex molecules.[2] Most examples of branched-selective hydroformylation make use of alkenes that have an electronic bias that encourages branched aldehyde formation. Thus some alkenes such as vinyl arene derivatives,[3] acrylic acid derivatives [4] and vinyl benzoates/acetates[5] almost exclusively form branched products. Alkenes of type $RCH_2CH{=}CH_2$ with a smaller electronic bias in the allylic position can also lead to some branched selectivity (60 to 90%).[6] Rh/BOBPHOS (Figure 1) catalysts appear to be unique, at present,[7,8] in that they are also able to give useful levels of branched regioselectivity[7] and enantioselectivity in hydroformylation of unbiased alkenes.

This type of branched selective hydroformylation is now being intensively investigated for the production of various industrial chemicals.[9] However, a significant extension would be if the unusual branched selectivity could be used advantageously in the synthesis of chiral building blocks for organic synthesis. Of special interest was to evaluate if functionalized but unbiased alkenes could be hydroformylated with branched regioselectivity, such that functionalized chiral heterocycles could be made. A further extension would be to investigate one-pot hydroformylation-cyclization reactions that could lead to these targets in an especially efficient way.

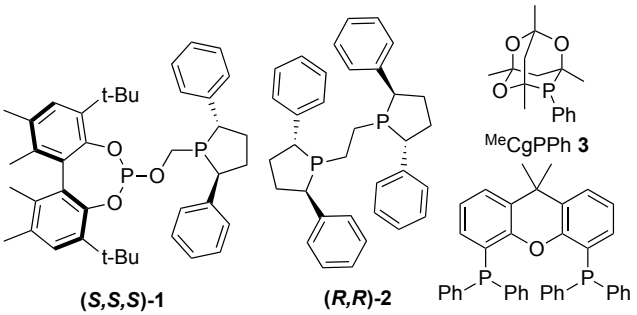
Here we report a study on the hydroformylation of various allylglycine derivatives, which enables an efficient synthesis of *tert*-butyl ((2*S*,4*S*)-1,5-dihydroxy-4-methylpentan-2-yl)carbamate **7,** used in the synthesis of the recently launched antibiotic Nemonoxacin **9** (Scheme 1).[10] We also demonstrate a tandem diastereoselective hydroformylation-hemiaminal formation reaction with branched regioselectivity to give functionalized piperidines.

Scheme 1. Synthesis of Nemonoxacin



We first investigated the hydroformylation of readily available allylglycine derivatives, benzyl-2-(1,3-dioxoisoindolin-2-yl)pent-4-enoate, **10a**, and benzyl-2-(dibenzylamino)pent-4-enoate, **11a** (*N*-Boc protected allylglycine esters could not be used). As shown in Table 1,

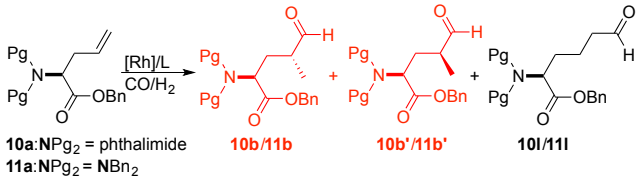
the use of various standard hydroformylation catalysts using ligands such as PPh_3, 1,3,5,7-tetramethyl-6-phenyl-2,4,8-trioxa-6-phosphaadamantane (^{Me}CgPPh),[11] XANTPHOS[1f,12] or Ph-BPE[13] do not give high yields of the desired isomer.



(*S,S,S*)-1 ((S_{ax},*S,S*)-BOBPHOS) **(*R,R*)-2** ((*R,R*)-Ph-BPE) (XANTPHOS) **4**

Figure 1. Ligands used in achiral and asymmetric hydroformylation

Table 1. Hydroformylation of benzyl -2-(1,3-dioxoisoindolin-2-yl)pent-4-enoate, 10a, and 2-(dibenzylamino)pent-4-enoate, 11a



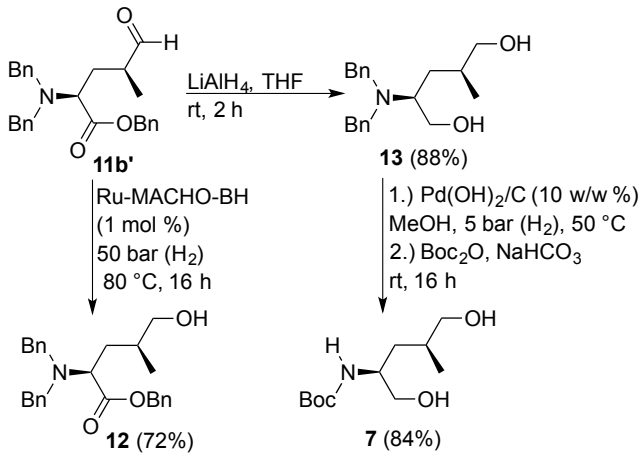
entry[a]	NPg	L	Temp (°C)	conv[b]	b:l	dr[c]
1	(*S*)-**10a**	dppf	40	0	-	-
2	(*S*)-**10a**	**4**[d]	40	8	0:1	-
3	(*S*)-**10a**	PPh_3	40	>99	1:1	61:39
4	(*S*)-**10a**	**3**	40	>99	0.8:1	61:39
5	(*S*)-**10a**	(*R,R*)-**2**	40	35	2.3:1	84:16
6	(*S*)-**10a**	(*R,R,R*)-**1**	40	>99	5.3:1	96:4
7	(*R*)-**10a**	(*R,R,R*)-**1**	25	48	1.9:1	74:26
8[e]	(*S*)-**10a**	(*R,R,R*)-**1**	25	92	6.8:1	98:2
9	(*S*)-**11a**	**3**	40	97	0.6:1	63:37
10	(*rac*)-**11a**	(*R,R,R*)-**1**	40	89	2.6:1	55:45
11	(*S*)-**11a**	(*R,R,R*)-**1**	40	92	2:1	92:8
12	(*R*)-**11a**	(*R,R,R*)-**1**	40	97	4:1	96:4
13[f]	(*S*)-**11a**	(*S,S,S*)-**1**	40	>99	4:1	94:6

(a) Standard reaction conditions, substrate (0.45 mmol), [Rh(acac)$(CO)_2$] = 0.4 mol%, L = 2 mol%, toluene, syngas used = 5 bar with BOBPHOS, 10 bar with all other ligands, time = 16 h (b) The reaction shows high chemoselectivity with mass balance being unreacted alkene, determined by 1H NMR, using I.S (1-methylnapthalene). (c) d.r = (*S,R*)-**10b**/(*S,S*)-**10b'** (for entries 3-6 & 8), (*R,R*)-**10b'**/(*R,S*)-**10b** (for entry 7), (*S,R*)-**11b**/(*S,S*)-**11b'** (for entries 9 and 11) or (*R,R*)-**11b'**/(*R,S*)-**11b** (for entry 12) (*S,S*)-**11b'**/(*S,R*)-**11b** (for entries 10 & 13) (d) See ref 12 (e) Isolated yield = 68% (f) Isolated yield = 62%

The results obtained using commercially available[7b] Rh / BOBPHOS are quite a contrast providing the correct enantiomer of BOBPHOS is matched with the correct enantiomer of the allylglycine derivative; there is a dramatic increase in branched selectivity (1.9:1 to 6.8:1), yield and diastereoselectivity (74:26 to 98:2) when using (*S*)-**10a**, as opposed to (*R*)-**10a**, if using Rh/(*R,R,R*)-**1** as the catalyst (entries 7 and 8, Table 1). The highest selectivity in the hydroformylation of (*S*)-**10a** led to (*S,R*)-**10b** as the major product. The same matching effect occurs in the dibenzyl protected amine, **11a**. The (*S,S,S*)-**1** catalyst is matched to the (*S*)-allylglycine derivative: this leads to the best selectivity and the diastereomer (*S,S*)-**11b'**, which is needed for the synthesis of the drug intermediate **7**.

Reduction of aldehydes **11b/11b'** to obtain the hydroxy-ester **12** was possible by hydrogenation catalysed by Ru-MACHO-BH,[14] with retention of stereochemistry (the compounds in Scheme 2 were all used as diastereomeric mixtures from the hydroformylation reactions of Table 1, entry 13). Hydrogenation of α-chiral aldehydes is generally quite challenging since typical catalysts for carbonyl reduction use basic conditions that cause racemization.[4a,14a] In studies on ester hydrogenation of either **10b**/**10b'** or **11b**/**11b'**, reduction of both aldehyde and ester group with retention was not possible (see supporting information (SI)). Reduction to the (*S,S*)-benzyl-diol **13**, was carried out easily with $LiAlH_4$, with full retention of stereochemistry. Debenzylation of the diol was successful using Pearlman's catalyst before reprotecting with di-*tert*-butyl dicarbonate. This gave *tert*-butyl ((2*S*,4*S*)-1,5-dihydroxy-4-methylpentan-2-yl)carbamate, **7** (Scheme 2), which is an intermediate enroute to Nemonoxacin **9**.

Scheme 2. Synthesis of *tert*-butyl ((2*S*,4*S*)-1,5-dihydroxy-4-methylpentan-2-yl)carbamate, 7

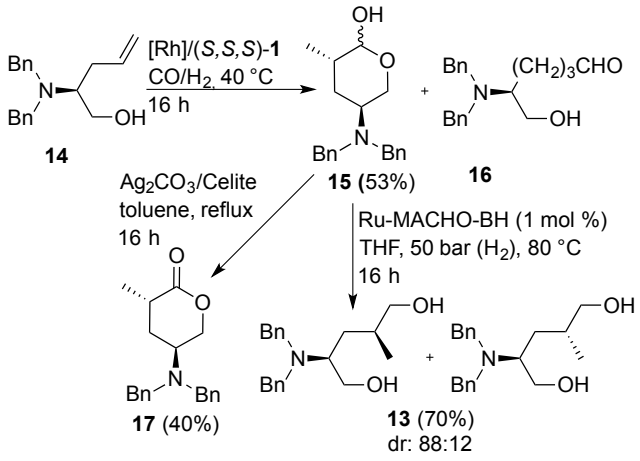


Tandem enantioselective hydroformylation-hemiacetal formation has rarely been observed,[6i,15] so we considered this as an alternative strategy. Tribenzylated allylglycine **11a**, could be successfully reduced to (*S*)-2-(dibenzylamino)pent-4-en-1-ol, **14**, using DIBAL-H in 91% yield (Scheme 3).[16] The hydroformylation of alcohol **14** can be performed selectively using either (*R,R,R*)-**1** or (*S,S,S*)-**1**. (*R,R,R*)-**1** obtains the best results in the hydroformylation of **14**, leading to 83% of the hemiacetal, **15**, with no branched aldehyde observed, and only 17% linear aldehyde (effective b:l 4.9:1); compared to 79% hemiacetal (effective b:l 3.8:1) when using (*S,S,S*)-**1** (ie -the opposite diastereomeric combination is matched compared to the studies on **11a**). The ratio of diastereomers in the hemiacetal mixture could not be determined by NMR.

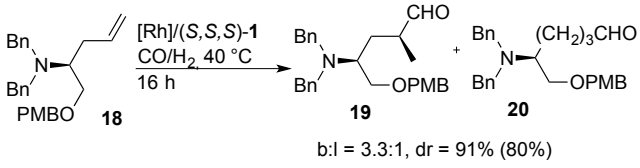
However oxidation of the crude hemiacetal mix delivered lactone **17**, and the ratio of diastereomers was found to be 93:7 when formed using (*R,R,R*)-**1** (88:12 when formed using (*S,S,S*)-**1**) by ^{1}H NMR.

To investigate if the hydroxyl moiety had an impact on the selectivity of the reaction, we hydroformylated the PMB (PMB = *p*-Methoxybenzyl) protected analogue, **18**. When (*S*)-*N,N*-dibenzyl-1-((4-methoxybenzyl)oxy)pent-4-en-2-amine **18** was subjected to our hydroformylation conditions, we found the selectivity was slightly less than that of its non-protected counterpart, obtaining b:l of 3.3:1 and 91% diastereoselectivity (Scheme 4). We note the branched selectivity is relatively similar to that obtained on a PMB protected homo-allyl alcohol that lacks the amino function, 1-((but-3-en-1-yloxy)methyl)-4-methoxybenzene, which gives 3.8:1 b:l selectivity and er of 94:6 (see SI). The higher regioselectivity and different matched combination of substrate and catalyst shows that the alcohol exerts some influence on the hydroformylation, perhaps by coordination to Rh.

Scheme 3. Tandem hydroformylation-hemiacetal formation and subsequent oxidation and hydrogenation.



Scheme 4. Hydroformylation of (*S*)-18.

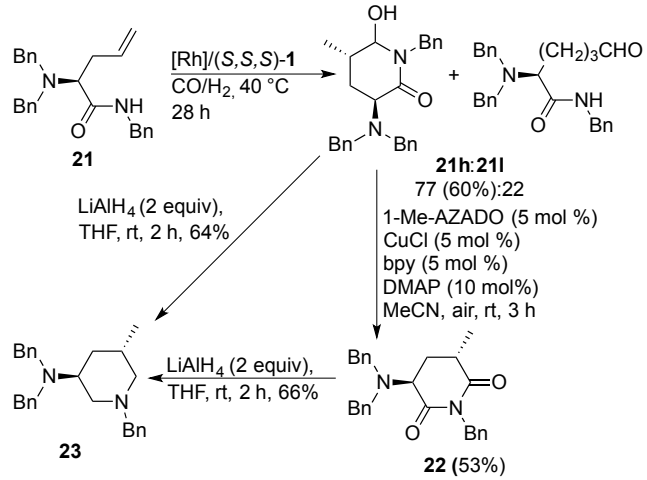


We were also pleased to find that the hemiacetal **15** could be hydrogenated using Ru-MACHO-BH[14] with retention of stereochemistry, since catalytic hydrogenation of an α-chiral hemiacetal does not seem to have been reported before. (2*S*,4*S*)-2-(dibenzylamino)-4-methylpentane-1,5-diol, **13**, utilized in the synthesis of Nemonoxacin, was isolated in 70% yield (with the ratio of diastereomers retained from the hydroformylation-hemi-acetal formation, Scheme 3).

Following the success of tandem hydroformylation-hemiacetal formation, we then considered a tandem hydroformylation-hemiaminal formation. While this work was in progress, the first report on tandem asymmetric hydroformylation-hemiaminal formation appeared, described as an 'interrupted hydroaminomethylation'. This important contribution makes use of substrates that are strongly biased towards branched aldehyde formation α- to an aromatic ring, and also requires a *N*-tosylate protecting group.[17] A tandem hydroformylation-hemiaminal formation that uses an unbiased alkene and delivers a very efficient synthesis of functionalized piperidines now seemed feasible due to the selectivity of [Rh]/BOBPHOS catalysts. Adapting a procedure by Huang et al[18] easily converted the (*S*)-benzyl ester derivative, **11a**, to (*S*)-*N*-benzyl-2-(dibenzylamino)pent-4-enamide **21** in a good yield (82%). The hydroformylation of this amide not only led to very good selectivity to the hemiaminal, **21h**, (<1% branched aldehyde, 22% linear aldehyde, **21l**) but also leads exclusively to essentially one diastereomer by ^{1}H NMR, when using (*S,S,S*)-BOBPHOS (Scheme 5). The reduction of the hemiaminal to the desired piperidine equivalent can be achieved in two different ways; the hemiaminal, **21h**, can be directly reduced using $LiAlH_4$, reducing both the amide and hemiaminal functionality, or the hemiaminal can be oxidized[19] to the dicarbonyl- derivative, **22**, which can be reduced using $LiAlH_4$ to the functionalized piperidine, **23**, (Scheme 5). Application of either oxidation or reduction to these substrates adds versatility to the chiral building blocks that can be synthesised using this methodology.

Using allylglycine as a starting material, which can be produced very efficiently using enzymatic methods,[20] the synthesis of *tert*-butyl ((2*S*,4*S*)-1,5-dihydroxy-4-methylpentan-2-yl)carbamate **7** has been achieved, which is a key intermediate in the synthesis of Nemonoxacin.[10] Tandem hydroformylation-cyclization reactions have also been developed for the synthesis of both functionalised piperidines and other 6-membered heterocycles. Despite the substrates used not being prone toward branched aldehyde formation, useful selectivity has been observed using the Rh/ BOBPHOS catalyst.

Scheme 5. Tandem hydroformylation-hemiaminal formation and subsequent oxidation and hydrogenation



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. (A PDF file containing full characterization data, NMR and HPLC spectra). The research data underpinning this article can be accessed at: http://dx.doi.org/10.17630/24f40cf5-ead3-4220-a297-881c40009402

AUTHOR INFORMATION

Corresponding Author

*Email: mc28@st-andrews.ac.uk

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Financial support by EPSRC (DTG grant: 1518070) and (EP/M0038868/1) is gratefully acknowledged.

REFERENCES

(1) (a) van Leeuwen, P. W. N. M.; Claver, C. *Rhodium Catalyzed Hydroformylation.;* James, B. R., van Leeuwen, P. W. N. M., Ed.; Kluwer Academic Publishers, The Netherlands, 2000, 22. (b) Franke, R.; Selent, D.; Börner, A. *Chem. Rev*. **2012**, *112*, 5675. (c) *Hydroformylation. Fundamentals, Processes, and Applications in Organic Synthesis.;* Börner, A.; Franke, R., Ed.; Wiley-VCH, Weinheim, Germany, 2016. (d) Casey, C. P.; Whiteker, G. T.; Melville, M. G.; Petrovich, L. M.; Gamey, J.; Powell, D. R. *J. Am. Chem. Soc*. **1992**, *114*, 5535. (e) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics*. **1995**, *14*, 3081.

(2) (a) Spangenberg, T.; Breit, B.; Mann, A. *Org. Lett.* **2009**, *11,* 261. (b) Dü bon, P.; Faewick, A.; Helmchen, G. *Synlett.* **2009**, *9,* 1413. (c) Guerlet, G.; Spangenberg, T.; Mann, A.; Faure, H.; Ruat, M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3608. (d) Botteghi, C.; Corrias, T.; Marchetti, M.; Paganelli, S.; Piccolo, O. *Org. Process Res. Dev*. **2002**, *6*, 379. (e) Botteghi, C.; Cazzaloto, L.; Marchetti, M.; Paganelli, S. *J. Org. Chem*. **1995**, *60*, 6612. (f) Cuny, G. D.; Buchwald, S. L. *J. Am. Chem. Soc*. **1993**, *115*, 2066. (g) Airau, E.; Spangenberg, T.; Breit, B.; Mann, A. *Org. Lett*. **2010**, *12*, 528.

(3) (a) Axtell, A. T.; Cobley, C. J.; Klosin, J.; Whiteker, G. T.; Zanotti-Gerosa, A.; Abboud, K. A. *Angew. Chem. Int. Ed*. **2004**, *44*, 5834. (b) Sakai, N.; Mano, S.; Nozaki, K.; Takaya*, H. J. Am. Chem. Soc.* **1993**, *115*, 7033. (c) Watkins, A. V.; Hashiguchi, B. G.; Landis, C. R. *Org. Lett*. **2008**, *10*, 4553.

(4) (a) Noonan, G. M.; Newton, D.; Cobley, C. J.; Surez, A.; Pizzano, A.; Clarke, M. L. *Adv. Synth. Catal.* **2010**, *352*, 1047. (b) Clarke, M. L.; Roff, G. J. *Green. Chem.* **2007**, *9*, 792; (c) Wang, A.; Buchwald, S. L.; *J. Org. Chem*. **2013**, 78, 3429.

(5) (a) Schmitz, C.; Holthusen, K.; Leitner, W.; Francio, G. *ACS Catal.* **2016**, *6*, 1584. (b) Nakano, K.; Tanaka, R.; Nozaki, K. *Helv. Chim. Acta*. **2006**, *89*, 1681. (c) Yan, Y.; Zhang, X. *J. Am. Chem. Soc.* **2006**, *128*, 7198. (d) Cobley, C.J.; Gardner, K.; Klosin, J.; Praquin, C.; Hill, C.; Whiteker, G. T.; Zanotti-Gerosa, A. *J. Org. Chem*. **2004**, *12*, 4031. (e) McDonald, R. I.; Wong, G. W.; Neupane, R. P.; Stahl, S. S.; Landis, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 14027; (f) Saidi, Q.; Ruan, J.; Vinci, D.; Wu, X.; Xiao, J. *Tetrahedron Lett*. 2008, 49, 3516; (g) Leigh-Abrams, M.; Foarta, F.; Landis, C. R. *J. Am. Chem. Soc.* **2014**, *136*, 14583; (h) Ho, S.; Bucher, C.; Leighton, J. L. *Angew. Chem. Int. Ed*. **2013**, *52,* 6757; (i) Grünanger, C. U. Breit, B. *Angew. Chem. Int. Ed*. **2010**, 49, 967.

(6) (a) Zhang, X.; Cao, B.; Yu, S.; Zhang X. *Angew. Chem. Int. Ed.* **2010**, *122*, 4141. (b) Yu, Z.; Eno, M. S.; Annis, A. H.; Morken, J. P. *Org. Lett*. **2015**, *17*, 3264. (c) Abrams, L. M.; Foarta, F.; Landis, C. R. *J. Am. Chem. Soc*. **2014**, *136*, 14583. (d) McDonald, R. I.; Wong, G. W.; Neupane, R. P.; Stahl, S. S.; Landis, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 14027. (e) Nanno, T.; Sakai, N.; Nozaki, K.; Takaya, I.; *Tetrahedron Asym*metry **1995**, *6*, 2583; (f) Joe, C. L.; Tan, K. L. *J. Org. Chem*. **2011**, *76*, 7590; (g) Joe, C. L.; Blaisdell, T. P.; Geoghan, A. F. Tan, K. L. *J. Am. Chem. Soc.* **2014***, 136,* 8556.

(7) (a) Noonan, G. N.; Fuentes, J.A.; Cobley, C. J.; Clarke, M. L. *Angew. Chem. Int. Ed*. **2012**, *51*, 2477. (b) (*S,S,S*)-BOBPHOS is commercially available from Strem Chemicals (Catalog #15-0557).

(8) An achiral catalyst has been reported to give selectively the branched (racemic) aldehydes desired from unbiased alkenes, with around 3:1 branched selectivity. (a) Besset, T.; Norman, D. W.; Reek, J. N. H. *Adv. Synth. Catal.* **2013**, *355*, 348. (b) Slagt, V. F.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *J. Am. Chem. Soc.* **2004**, *126*, 1526.

(9) (a) Noonan, G. M.; Cobley, C. J.; Mahoney, R.; Clarke, M. L. *Chem. Commun*. **2014**, *50,* 1475. (b) Fuentes, J.; Pittaway, R.; Clarke, M. L. *Chem. Eur. J*. **2015**, *21*, 10645. (c) C. How, R. C.; Hembre, R.; Ponasik, J. A.; Tolleson, G. S; Clarke, M. L. *Catal. Sci. Technol*. **2016**, *6*, 118.

(10) (a) Crasto, A. (2017). New Drug Approvals. Available at: https://newdrugapprovals.org/2014/03/18/ nemonoxacin-taigens-pneumonia-antibiotic-taigexyn-%E5%A5%88 %E8%AF%BA%E6%B2%99%E6%98%9F-gets-marketing-approval-in-taiwan/. (b) Guo, B.; Wu, X.; Zhang, Y.; Shi, Y.; Yu, J.; Cao, G.; Zhang, J. *Clin. Dru. Inves*. **2012**, 32, 475.

(11) (a) Baber, R. A.; Clarke, M. L.; Heslop, K.; Marr, A.; Orpen, A. G.; Pringle, P.G.; Ward, A. M.; Zambrano-Williams, D. A. *Dalton Trans*. **2005**, 1079. (b) Clarke, M. L.; Roff, G. J. *Chem. Eur. J.* **2006**, *12*, 7978.

(12) Using XANTPHOS for the hydroformylation of (*S*)-**11a**, (CO/H_2 (20 bar), 40 °C, 96 h) full conversion to the linear aldehyde was obtained. Rodriquez, M.; Bruno, I.; Cini, E.; Marchetti, M.; Taddei, M.; Gomez-Paloma, L. *J. Org. Chem.* **2006**, *71*, 103.

(13) Pilkington, C. J.; Zanotti-Gerosa, A. *Org. Lett.* **2003***, 5*, 1273.

(14) (a) Kuriyama, W.; Matsumoto, T.; Ogata, O.; Ino, Y.; Aoki, K.; Tanaka, S.; Ishida, K.; Kobayashi, T.; Sayo, N.; Saito, T. *Org. Process Res. Dev.* **2012**, *16*, 166. (b) Ru-MACHO-BH is commercially available from Strem (Catalog # 44-0074). For structure, see SI.

(15) (a) Nozaki, K.; Li, W.; Horiuchi, T.; Takaya, H. *Tet. Lett*. **1997**, *38*, 4611; (b) Rodrigues, C.; Delolo, F. G.; Norinder, J.; Börner, A.; Bogado, A. L.; Batista, A. A. *J. Mol. Catal*. **2017**, *426*, 586.

(16) Tamamura, H.; Yamashita, M.; Nakajima, Y.; Sakano, K.; Otaka, A.; Ohno, H.; Ibuka, T.; Fujii N. J. *Chem. Soc., Perkin Trans.* **1999**, *1*, 2983.

(17) (a) Chen, C.; Jin, S.; Zhang, Z.; Wei, B.; Wang, H.; Zhang, K.; Lv, H.; Dong, X.; Zhang, X. *J. Am. Chem. Soc.* **2016**, *138*, 9017; (b) Hydroformylation + tandem organocatalytic D.K.R. reductive amination using Hantzch ester reductant: Meng, J.; Li, X-H.; Han, Z-Y. *Org. Lett*. **2017**, *19*, 1076; (c) Villa-Marcos, Xiao, J. *Chin. J. Catal*. **2015**, *36*, 261.

(18) Huang, P-Q.; Zheng, X.; Deng, X-M. *Tet. Lett*. **2001**, *42*, 9039.

(19) Sasano, Y.; Nagasawa, S.; Yamazaki, M.; Shibuya, M.; Park, J.; Iwabuchi, Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 3236.

(20) (a) Baxter, S.; Royer, S.; Grogan, G.; Brown, F.; Holt-Tiffin, K. E.; Taylor, I. N.; Fotheringham, I. G.; Campopiano D. J. *J. Am. Chem. Soc.* **2012**, *134*, 19310. (b) Baxter, D.; Campopiano, D. J.; Holt-Tiffin, K. E. U.S. Patent 14 009 758, 2014. (c) Krishnamurthy, S.; Arai, T.; Nakanishi, K.; Nishino N. *RSC Adv.* **2014**, *4*, 2482.