Tetrahedron Letters 51 (2010) 4214–4217

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis and use of a stable aminal derived from TsDPEN in asymmetric organocatalysis

Silvia Gosiewska, Rina Soni, Guy J. Clarkson, Martin Wills *

Department of Chemistry, The University of Warwick, Coventry CV4 7AL, UK

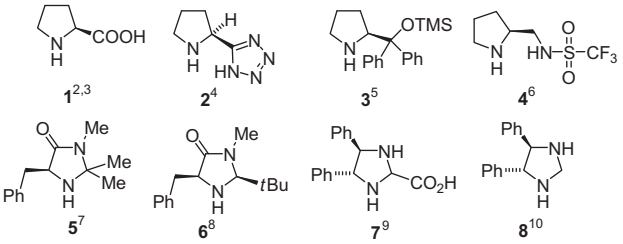
ARTICLE INFO

Article history:
Received 1 April 2010
Revised 27 May 2010
Accepted 4 June 2010
Available online 9 June 2010

ABSTRACT

A stable aminal formed stereoselectively from (*R*,*R*)-*N*-tosyl-1,2-diphenyl-1,2-ethylenediamine (TsDPEN) is capable of asymmetric organocatalysis of Diels–Alder and α-amination reactions of aldehydes.

The use of enantiomerically pure amines as catalysts for organic reactions has proved to be a productive area of research.[1–10] Following initial reports on the use of proline,[2] several derivatives based on five-membered N-containing rings have been developed, notably pyrrolidine derivatives such as **1–4**.[3–6] Closely related cyclic aminals, such as **5**–**8**, have also been successfully applied.[7–10] Imidazolidinones **5** and **6** generate high enantioselectivity in, for example, Diels–Alder additions, α-chlorination of ketones, Michael additions, conjugate hydride additions to enones and aldol reactions.[7,8] Aminals **7** and **8** have been employed in asymmetric α-amination and bromination of ketones and nucleophilic additions to enones.[9,10] In this Letter, we describe the synthesis of a novel class of homochiral aminal which shows activity in asymmetric organocatalytic reactions.

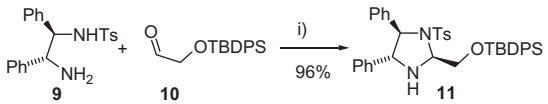


1[2,3] **2**[4] **3**[5] **4**[6] **5**[7] **6**[8] **7**[9] **8**[10]

During the course of studies on the functionalisation of (*R*,*R*)-*N*-tosyl-1,2-diphenyl-1,2-ethylenediamine (TsDPEN) **9** via reductive alkylation,[11] we found that its reaction with α-trialkylsilyloxy-substituted aldehyde **10** resulted in the formation of stable aminal **11**. This was not reduced in situ under conditions which we had typically used for reductive alkylation, for example, $NaBH_3CN$, MeOH.[11] Although aminal **11** could be reduced to the required product **12** (the TBDPS group was also removed in this process) using $LiAlH_4$, it could also be readily purified by flash chromatography without hydrolysis. Significantly, **11** was formed as a single diastereoisomer in high yield upon acid-catalysed reaction of **9** with **10** (Scheme 1). X-ray crystallographic analysis of a purified sample (Fig. 1) revealed the relative stereochemistry illustrated, that is, with the TBDPS group trans to the phenyl adjacent to the basic amine.

Given the structural similarity of **11** to related organocatalysts such as **5**–**8**,[7–10] we chose to investigate its ability to act in this capacity. In the Diels–Alder reaction (Scheme 2, Table 1) between cyclohexadiene and acrolein,[7a] using 10 mol % of **11** as its hydrochloride salt, the predominant *endo* cycloaddition product was formed in up to 72% ee. Full conversion was achieved under optimised conditions (see Supplementary data for full details). The use of the salt is important; the free base gave no conversion at 5% catalyst loading, although 23% of racemic product was formed after 24 h using 10 mol % of **11**.[7a] The presence of a small amount of water in the solvent increases the rate of the reaction but does not reduce the selectivity. The product was shown to be of *S* configuration at the atom adjacent to the aldehyde group by reduction of a sample of 72% ee to the corresponding alcohol and comparison of the sign of the optical rotation to that reported for this compound.[12] This configuration would mirror that of close precedents[7a] in the literature which indicates that the cycloaddition takes place through an *endo* transition state to the *E*-iminium cation on the less hindered face (Fig. 2).

Encouraged by this result, we sought to establish whether aminal **11** remained intact under the reaction conditions or degraded (for example, by hydrolysis) to TsDPEN **9**. The use of TsDPEN·HCl (**9**·HCl) under the same conditions gave a cycloaddition product



9 **10** **11**

Scheme 1. Reagents: (i) AcOH, reflux.

* Corresponding author. Tel.: +44 24 7652 3260; fax: +44 24 7652 4112.
E-mail address: m.wills@warwick.ac.uk (M. Wills).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.06.017

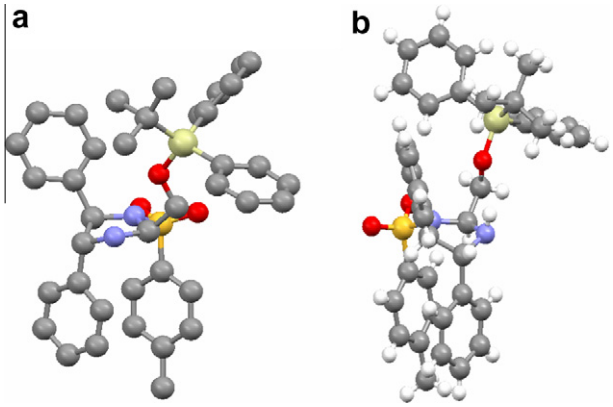
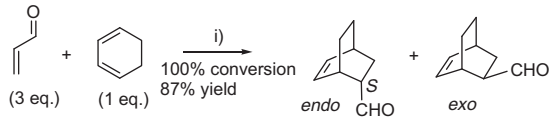
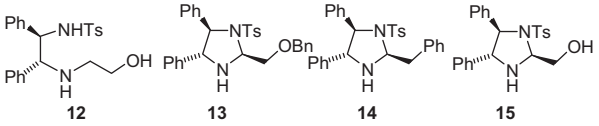


Figure 1. X-ray structure of **11** (CCDC 767194). (a) H atoms removed for clarity, (b) with H atoms shown.



Scheme 2. Reagents and conditions: (i) 10 mol % **11**·HCl, 95:5 MeCN/H_2O.

of just 28% ee (*endo*:*exo* 10:1.5, 87% conversion in 22.5 h). The reaction of **11** with excess acrolein gave no evidence of exchange of aldehyde with the aminal. In order to establish the importance of the silyloxy group, the analogues **13** and **14** were also prepared from TsDPEN and the corresponding aldehydes. Desilylation of **11** gave **15** in 85% yield, which was also tested.



Benzyloxy derivative **13** proved to be stable and was readily purified in single diastereoisomer form (relative configuration assigned by analogy with **11**). In contrast, the benzyl derivative **14** was prepared in low yield as a mixture of diastereomers from which the major (relative configuration unknown) was purified by chromatography on silica gel.

The use of aminal **14** in the cycloaddition reaction (Scheme 2) gave a product with an ee similar to that obtained with **9**·HCl, and could not be recovered after the reaction, thus suggesting that it may be hydrolysed (**9** was detected by TLC). In contrast, all the alkoxy- and hydroxy-derivatives could be reisolated from the reaction and reused. An attempt to prepare an aminal from TsDPEN and benzaldehyde did not give the required product. This difference in stability may be a result of the electron-withdrawing effect of the alkoxy group. The benzyloxy catalyst **13** gave a cycloaddition product of 45% ee and the hydroxy catalyst **15**, one of 44% ee, indicating that the bulkier TBDPS group is advantageous to the reaction selectivity. An attempt was made to form an aminal from *trans*-*N*-tosyl-1,2-cyclohexanediamine, however, this failed, possibly due to a high level of strain in the bicyclic product.

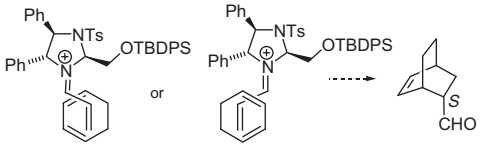
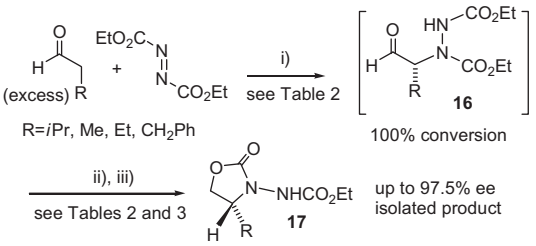


Figure 2. Control of selectivity of the Diels–Alder cycloaddition using **11**. Cyclohexadiene adds to the least hindered face of each conformer of the *E*-iminium cation.



Scheme 3. Reagents and conditions: (i) 2–10 mol % **11**, **9**, **13**–**15** RCO_2H, neat; (ii) $NaBH_4$; (iii) NaOH.

The application of aminals **11** and **13**–**15** to a series of other asymmetric organocatalytic reactions was investigated. Of these, promising results were obtained in the asymmetric addition of diethylazodicarboxylate (DEAD) (Scheme 3)[3a,b,9a] in which addition products of up to 97.5% ee were isolated using 10 mol % of **11**. Using a relatively non-volatile aldehyde, that is, 3-methylbutanal, in initial studies (Table 2) and **11** as the catalyst, the addition of a small amount of AcOH was found to be advantageous to the reaction rate, although the ee was not affected.

Whilst 100% conversion of DEAD (limiting reagent) to **16** was observed by NMR, this product was not isolated because it was prone to racemisation. Instead, **16** was reduced and cyclised to the configurationally stable oxazolidinone **17** in order to establish the ee.[3b] Since the reactions were followed by taking samples at intervals (see Supplementary data for graphs), the isolated yields of **16** and **17** were not recorded at this stage.

Table 1
Diels–Alder reaction of acrolein and 1,3-cyclohexadiene using catalysts **11**, **9** and **13**–**15**·HCl

Entry	Catalyst	mol %	Solvent	*t* (h)	Conv.[a] (%)	Yield[b] (%)	*endo*:*exo*	ee[c] (%) (*endo*)
1	**11**·HCl	5	CH_3CN/H_2O (95:5)	48	83	38	12:1	67
2	**11** (free base)	5	CH_3CN/H_2O (95:5)	24	0	—	—	—
3	**11**·HCl	10	CH_3CN/H_2O (95:5)	24	100[d]	87	10:1	72
4	**11**·HCl	15	CH_3CN/H_2O (95:5)	16	93	80	8:1	71
5	**11**·HCl	5	CH_3CN (dry)	180	83	65	10:1	67
6	**9**·HCl	10	CH_3CN/H_2O (95:5)	22.5	87	28	7:1	28
7	**13**·HCl	10	CH_3CN/H_2O (95:5)	17	100[d]	35	10:1	45
8	**14**·HCl	10	CH_3CN/H_2O (95:5)	17	100[d]	35	5:1	29
9	**15**·HCl	10	CH_3CN/H_2O (95:5)	18.5	100[d]	36	12:1	44

[a] Conversion calculated from the ^1H NMR spectrum of the reaction mixture.
[b] Isolated yield by column chromatography.
[c] %ee determined by chiral GC of the purified *endo* product [115 °C, t_R 43.14 (minor) and 44.64 min (major)].
[d] No 1,3-cyclohexadiene signals were detected by ^1H NMR spectroscopy.

Table 2
Reaction of DEAD with 3-methylbutanal catalysed by **11**; variation of acid level, catalyst loading and acid[a]

Entry	mol % **11**	mol % Acid (AcOH unless stated)	Time[b] (h)	Temp	ee[c]
1	10	0	10.0	rt	96.2 (*R*)
2	10	5	6.0	rt	97.2 (*R*)
3	10	10	4.5	rt	96.6 (*R*)
4	10	15	4.5	rt	96.0 (*R*)
5	10	20	4.5	rt	95.6 (*R*)
6	10	10	3.0	40 °C	93.4 (*R*)
7	10	10	24.0	0–5 °C	97.5 (*R*)
8	5	5	23.5	rt	96.3 (*R*)
9	2	2	30.0	rt	nd[d]
10	10	10 CF_3CO_2H	3.0	rt	71.7 (*R*)
11	10	10 $PhCO_2H$	6.0	rt	96.2 (*R*)
12	10	10 4-$NO_2C_6H_4CO_2H$	6.0	rt	96.0 (*R*)
13[e]	10	10	5/20/24	rt	96.0 (*R*)
14[f]	10	10	5/17/24	rt	95.6 (*R*)

[a] Aldehyde = 3-methylbutanal, catalyst (*R*,*R*)-**11**, DEAD, no solvent, reactions were all followed by ^{1}H NMR (see Supplementary data for plots).
[b] Time at which 100% conversion was observed by ^{1}H NMR.
[c] ee of cyclised product **17** after reduction of **16**.
[d] nd = not determined, decomposition of DEAD was observed.
[e] Three cycles of aldehyde and DEAD addition, without extra AcOH; ee given for last run.
[f] Three cycles of aldehyde, DEAD and AcOH addition; ee given for last run.

Table 3
Comparison of catalysts with and without AcOH; propanal addition[a]

Entry	Catalyst	Diimide	AcOH (%)	Time[b]	Yield[c]	ee (**17**)
1	RR **11**	DEAD	0	2 h	47%	97% (*R*)
2	RR **11**	DEAD	10	110 min	55%	95% (*R*)
3[e]	RR **9**	DEAD	0	47 h	42%	32% (*R*)
4	RR **9**	DEAD	10	45 min	66%	49% (*R*)
5	RR **13**	DEAD	0	44 h	46%	62% (*R*)
6	RR **13**	DEAD	10	45 min	66%	90% (*R*)
7	RR **14**	DEAD	10	115 min	crude	84% (*R*)
8	RR **15**	DEAD	0	5 d	0[d]	nd[f]
9	RR **15**	DEAD	10	31 h	37%	61% (*R*)
10	RR **11**	DiPrAD	0	22.5 h	99%	nd[f]
11	RR **11**	DtBuAD	0	70.5 h	68%	nd[f]

[a] Aldehyde = propanal, 10 mol % catalyst, rt in all cases, neat unless otherwise stated.
[b] Time at which 100% conversion was observed by ^{1}H NMR.
[c] Isolated yield of cyclised product **17** after reduction of **16**.
[d] No reaction observed.
[e] In CH_2Cl_2 solvent.
[f] nd = not determined.

At rt (20–25 °C), using 10 mol % of **11**, the reaction was complete in 4.5 h, whilst at slightly elevated temperature the reaction was faster but the ee was lower (entry 6). As anticipated, the reversed trend was seen at lower temperature (entry 7) which gave the highest measured ee. The amount of catalyst **11** could be reduced to 5 mol % without loss of enantioselectivity, however, at 2 mol % the reaction was significantly slower and competing decomposition of DEAD was observed. A number of alternative acids were investigated (entries 10–12), with the strongest acid, TFA giving the shortest reaction time, but products of lower ee were formed. Finally, the repeated addition of substrate (both with and without extra acid; entries 13 and 14) was tested and revealed that the catalyst continued to promote the addition in high enantioselectivity, although the reaction time increased with each addition. The lower reactivity, but retained high ee, suggests that catalyst inhibition may be taking place, rather than hydrolysis, since TsDPEN was found to give a product of much lower ee (see below). Having established satisfactory conditions, a series of catalysts were evaluated, this time with propanal as the aldehyde, both with and without added acetic acid and with variation of the dialkyldiazodicarboxylate (Table 3).

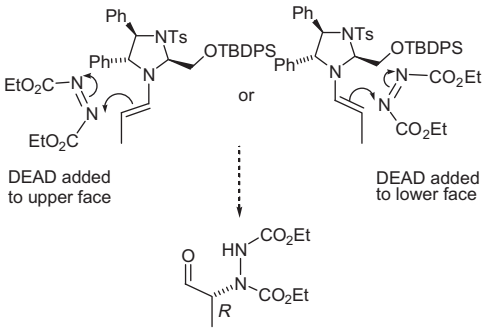


Figure 3. Addition of DEAD to an *E*-enamine with blocking of one face by substituents on the heterocyclic ring of **11**.

After completion of the reaction (Scheme 3) the aldehyde was immediately reduced and cyclised to **17**, for which isolated yields are given. In each case, the addition of AcOH significantly reduced the reaction time required for 100% conversion of DEAD to product. Aminal **11** gave the best results, and TsDPEN **9** gave the product in up to 49% ee. The use of the *i*Pr and *t*Bu versions of DEAD gave products in good yields but after much longer reaction times. Enantiomeric excesses were not determined in these cases. The reaction was extended to alternative carbonyl substrates, which gave mixed results. The addition of butanal and 3-phenylbutanal worked well, giving products in 97% and 84% ee, respectively (*R* enantiomers) (see Supplementary data).

The formation of the product of *R* configuration using catalyst **11** suggests a reaction via an *E*-enamine, *trans* either to the OTBDPS group or to the phenyl ring on the other side of the heterocyclic ring, depending upon the conformation of the intermediate enamine (Fig. 3). This would be consistent with the directing effects observed using diarylprolinol catalysts in which the substituent on the pyrrolidine ring acts as a blocking group to electrophile addition.[13] The observation of the same sense of induction with catalyst **15** also suggests that the hydroxymethyl group is not directing the addition, that is, via a hydrogen bond. Attempts to catalyse the addition of the α-branched aldehydes formylcyclohexane and 2-methylpropanal (i.e., a non asymmetric addition) and ketones (acetone and cyclohexanone) to DEAD were unsuccessful.

In conclusion, we have demonstrated that a stable aminal derived from TsDPEN **9** can be used as a catalyst for asymmetric C–C and C–N bond-forming reactions.

Acknowledgements

We thank Warwick University for financial support (Warwick Postgraduate Research Studentship to R.S.) and EPSRC for financial support (Grant No. EP/D031168/1 to S.G.). Dr. B. Stein and colleagues of the EPSRC National MS service (Swansea) are thanked for HRMS analyses. We acknowledge the use of the EPSRC Chemical Database Service.[14] The Oxford Diffraction Gemini instrument was obtained through the Science City Project with support from the Advantage West Midlands (AWM) Advanced Materials Project and part funded by the European Regional Development Fund (ERDF).

A. Supplementary data

Supplementary data (experimental details, X-ray data, NMR and HPLC spectra, and graphs of experimental results) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.017.

References and notes

1. (a) Xu, L.-W.; Lu, Y. *Org. Biomol. Chem.* **2008**, *6*, 2047–2053; (b) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138–6171; (c) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638–4660; (d) Connon, S. J. *Chem. Commun.* **2008**, 2499–2510; (e) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724; (f) Erkkila, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416–5470; (g) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569; (h) Lattanzi, A. *Chem. Commun.* **2009**, 1452–1463; (i) Xu, L.-W.; Luo, J.; Lu, Y. *Chem. Commun.* **2009**, 1807–1821; (j) MacMillan, D. W. C. *Nature* **2008**, *455*, 304–308.
2. (a) Eder, U.; Sauer, G.; Weichert, R. *Angew. Chem., Int. Ed Engl.* **1971**, *10*, 496–497; b Hajos, Z. G.; Parrish, D. R. German Patent DE 2102623, 1971; *Chem. Abstr.* **1972**, *76*, 59072.; (c) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621.
3. (a) Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254–6255; (b) Bøgevig, A.; Juhl, K.; Kumaragurubaran, N.; Zhuang, W.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1790–1793; (c) List, B.; Lerner, R. A.; Barbas, C. F., III *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396.
4. (a) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84–96; (b) Cobb, A. J. A.; Longbottom, D. A.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2004**, 1808–1809.
5. (a) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212–4215; (b) Gu, Q.; Wang, X. F.; Wang, L.; Wu, X. Y.; Zhou, Q. L. *Tetrahedron: Asymmetry* **2006**, *17*, 1537–1540.
6. (a) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1369–1371; (b) Yang, H.; Carter, R. G. *Org. Lett.* **2008**, *10*, 4629–4652; (c) Mei, K.; Zhang, S.; He, S.; Li, P.; Jin, M.; Xue, F.; Luo, G.; Zhang, H.; Song, L.; Duan, W.; Wang, W. *Tetrahedron Lett.* **2008**, *49*, 2681–2684.
7. (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244; (b) Kristensen, T. E.; Vestli, K.; Hansen, F. K.; Hansen, T. *Eur. J. Org. Chem.* **2009**, *30*, 5185–5191; (c) Barykina, O. V.; Rossi, K. L.; Rybak, M. J.; Snider, B. B. *Org. Lett.* **2009**, *11*, 5334–5337; (d) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108–4109; (e) Peelen, T. J.; Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, *127*, 11598–11599.
8. (a) Mangion, I. K.; Northrup, A. B.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 6722–6724; (b) Contad, J. C.; Kog, J.; Laforteza, B. N.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 11640–11641; (c) Adolffsson, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 3340–3342; (d) Nagib, D. A.; Scott, M. E.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 10875–10877; (e) Nicewicz, D. A.; Macmillan, D. W. C. *Science* **2008**, *322*, 77–80.
9. (a) Kotrusz, P.; Alemayehu, S.; Toma, S.; Schmalz, H.-G.; Adler, A. *Eur. J. Org. Chem.* **2005**, 4904–4911; (b) Halland, N.; Hansen, T.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4955–4957.
10. Bertelsen, S.; Halland, N.; Bachmann, S.; Marigo, M.; Braunton, A.; Jørgensen, K. A. *Chem. Commun.* **2005**, 4821–4823.
11. Martins, J. E. D.; Clarkson, G. J.; Wills, M. *Org. Lett.* **2009**, *11*, 847–850.
12. Cervinka, O.; Kriz, O. *Collect. Czech. Chem. Commun.* **1968**, *33*, 2342–2345.
13. Franzen, J.; Marigo, M.; Fielenbch, D.; Wabnitz, T. C.; Kjaersgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304.
14. Fletcher, D. A.; McMeeking, R. F.; Parkin, D. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746–749.