VAPOL phosphoric acid catalysis: the highly enantioselective addition of imides to imines†

Yuxue Liang, Emily B. Rowland, Gerald B. Rowland, Jason A. Perman and Jon C. Antilla*

Received (in Cambridge, UK) 20th June 2007, Accepted 6th August 2007
First published as an Advance Article on the web 21st August 2007
DOI: 10.1039/b709276h

The first highly enantioselective catalytic method for the preparation of chiral aminals *via* the addition of imide nucleophiles to imines is reported.

Over the last twenty years the adoption of new catalytic processes with efficient stereocontrol for the synthesis of pharmaceuticals has found a steady increase in the fine chemicals industry. A recent analysis of the preparation of potential drug candidates indicates that >90% of these molecules contain nitrogen and 54% are chiral.[1] Furthermore, in this analysis an investigation of the methodology employed in the synthesis of such compounds by three major pharmaceutical companies show that 19% of the reactions used were carbon–heteroatom bond-forming reactions involving alkylation or arylation. It is therefore important that new stereoselective carbon–heteroatom bond forming reactions be developed so diverse structures can be readily accessed. We wish to report a method whereby imides can be added efficiently and with notable enantiocontrol to imine electrophiles for the preparation of chiral *geminal* diamines.

In 2005, we reported the first catalytic asymmetric method whereby sulfonamides can be added to imines to provided chiral aminals (*gem*-diamines) in high yield and enantiomeric excess (ee).[2a] However, this methodology was limited to sulfonamide nucleophiles, with other amides providing lower enantioselectivity in the process. We believed that with more suitable protecting groups on the nitrogen atoms of the aminal the incorporation of chiral aminals into peptide structure could follow similar procedures developed by Goodman[3] and others[4] to provide *retro-inverso* peptide mimics. Additionally, we believe that through this type of methodology the assembly of various core chiral aminal subunits found in natural products[5] and pharmaceuticals[6] could be accessed.

As a part of our ongoing studies using chiral phosphoric acids as organocatalysts[2] we sought to develop additional protocols whereby heteroatom nucleophiles could be added to electrophiles in high yielding and enantioselective reactions. We found, initially, that despite high yields for various nitrogen nucleophiles, our enantioselectivities were quite limited. However, as we continued to screen potential nucleophiles we discovered that imides were suitable substrates for heteroatom additions. We determined that the use of hindered BINOL phosphoric acids **PA2–4**[7] (Fig. 1) could provide increasing enantioselectivities for the addition of

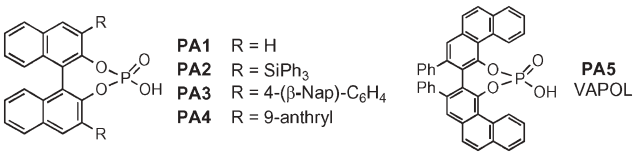
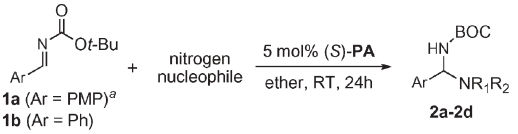


Fig. 1 Chiral phosphoric acid catalysts.

phthalimides to **1a** (Table 1, entries 1–4). The use of a phthalimide protected amine should allow for the differential deprotection of either nitrogen of the aminal, allowing for the synthesis of derivatives.[8] We were pleased to find that the VAPOL derived phosphoric acid **PA5** catalyzed the addition of phthalimide provided for the desired product in excellent yield and enantioselectivity (entry 5). This result is the first example in the literature where an imide is shown to add in a 1,2-fashion to an imine with high enantioselectivity.[9] The use of simple amides as nucleophiles under these conditions gave satisfactory yields but poor enantioselectivities (entries 6–8).

In an effort to show the generality of the imide additions a series of aryl substituted imines were prepared and evaluated for the chemistry. To our delight, we observed broad substrate scope with respect to aryl and substituted aryl imines for the addition of phthalimides (Table 2). Electron donating substituents in the *ortho* (entries 3 and 6), *meta* (entry 4), or *para* (entries 1 and 5) were all shown to be excellent substrates for the addition. Likewise, the use of electron withdrawing substituents (entries 7–9) on the *para*

Table 1 Catalyst optimization for the enantioselective addition of amides and imides to *N*-BOC imines



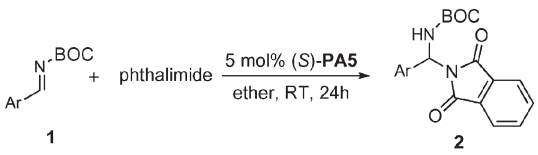
Entry	Ar	Nucleophile	(*S*)-PA	Product	Yield,%[b]	ee,%[c]
1	**1a**	phthalimide	**PA1**	**2a**	31	0
2	**1a**	phthalimide	**PA2**	**2a**	80	56
3	**1a**	phthalimide	**PA3**	**2a**	76	34
4	**1a**	phthalimide	**PA4**	**2a**	82	47
5	**1a**	phthalimide	**PA5**	**2a**	92	96
6	**1a**	$PhC(O)NH_2$	**PA5**	**2b**	90	34
7	**1b**	$MeC(O)NH_2$	**PA5**	**2c**	89	18
8	**1b**	acrylamide	**PA5**	**2d**	96	21

[a] PMP = 4-$MeOC_6H_4$ group. [b] Isolated yields. [c] Enantiomeric excess (ee) was determined by chiral HPLC and in each case was compared to the respective racemate.

Department of Chemistry, University of South Florida, 4202 E. Fowler Ave., Tampa, FL 33620, USA. E-mail: jantilla@cas.usf.edu; Fax: (1) 813 974 1733; Tel: (1) 813 974 7438

† Electronic supplementary information (ESI) available: experimental procedures and characterization data for unknown compounds. See DOI: 10.1039/b709276h

Table 2 The catalytic asymmetric addition of substituted phthalimides to *N*-BOC imines **1a–1j**



Entry	Imine: Ar	Product	Yield,%[a]	ee,%[b]
1	**1a** = 4-MeOC$_6$H$_4$	**2a**	92	96
2	**1b** = Ph	**2e**	88	93
3	**1c** = 2-MeC$_6$H$_4$	**2f**	94	99
4	**1d** = 3-MeC$_6$H$_4$	**2g**	86	90
5	**1e** = 4-MeC$_6$H$_4$	**2h**	90	94
6	**1f** = 2-MeOC$_6$H$_4$	**2i**	91	93
7	**1g** = 4-ClC$_6$H$_4$	**2j**	93	93(*R*)[c]
8	**1h** = 4-BrC$_6$H$_4$	**2k**	87	90
9	**1i** = 4-FC$_6$H$_4$	**2l**	90	93
10	**1j** = 1-Naph	**2m**	86	91

[a] Isolated yields. [b] Enantiomeric excess (ee) was determined by chiral HPLC and in each case was compared to the racemate. [c] The absolute configuration of **2j** was determined by X-ray crystallographic analysis.[9]

position of the phenyl-substituted imines gave a substrate that allowed for high yield and enantiomeric excess upon addition. The relatively sterically hindered 1-naphthyl substituted imine **1j** (entry 10) was also an excellent substrate, allowing for the preparation of **2m** in an 86% yield with a 91% ee.

The absolute configuration of **2j** was determined to be (*R*) by X-ray crystallographic determination methods (Fig. 2).[10]

The substrate generality with respect to the imide was evaluated using a series of substituted phthalimides and maleimide (Table 3). The addition employing maleimide proceeded under the general reaction conditions to provide an 82% yield of the respective aminal **2n** with an enantioselectivity of 92% (entry 2). Likewise, both 3-methyl and 4-methylphthalimide were also shown to be effective reaction partners, both providing good yields and enantioselectivities (entries 3–4). Electron withdrawing substituents were not problematic in the case of phthalimides, with 4-chloro, 4-bromo, 4-fluoro, and 3-fluorophthalimide providing 89–93% ee with satisfactory yields of the respective aminal products in each case (entries 5–8).

In summary, we have developed the first method whereby imides can be added to imines with high enantioselectivity and in good yield using a chiral VAPOL phosphoric acid catalyst. The

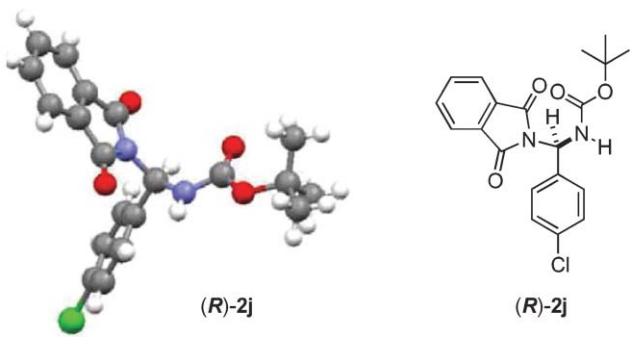
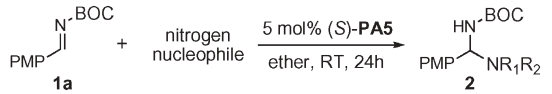
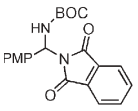


Fig. 2 X-ray crystal structure of (*R*)-**2j**.

Table 3 The catalytic asymmetric addition of substituted imides to **1a**

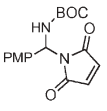


entry 1: product **(2a)**[a]



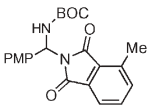
92% yield, ***96% ee***

entry 2: product **(2n)**



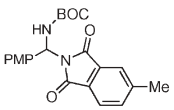
82% yield, ***92% ee***

entry 3: product **(2o)**



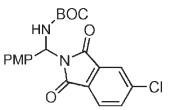
82% yield, ***92% ee***

entry 4: product **(2p)**



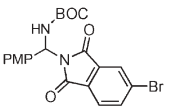
90% yield, ***92% ee***

entry 5: product **(2q)**



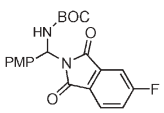
92% yield, ***93% ee***

entry 6: product **(2r)**



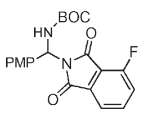
84% yield, ***90% ee***

entry 7: product **(2s)**



87% yield, ***91% ee***

entry 8: product **(2t)**



84% yield, ***89% ee***

[a] Isolated yields were obtained for all products.

reaction was shown to be general in terms of the imine and phthalimide substrates. Future work will include practical applications of the methodology to the construction of chiral aminals contained in potentially pharmacologically active substances. Mechanistic studies are ongoing, and should provide insight into the basis of the catalysis.

Notes and references

1 J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, *Org. Biomol. Chem.*, 2006, **4**, 2337.

2 (*a*) G. B. Rowland, H. Zhang, E. B. Rowland, S. Chennamadhavuni, Y. Wang and J. C. Antilla, *J. Am. Chem. Soc.*, 2005, **127**, 15696; (*b*) G. Li, Y. Liang and J. C. Antilla, *J. Am. Chem. Soc.*, 2007, **129**, 5830; (*c*) G. B. Rowland, E. B. Rowland, Y. Liang, J. A. Perman and J. C. Antilla, *Org. Lett.*, 2007, **9**, 2609.

3 For review articles by M. Goodman see: (*a*) M. Goodman and M. Chorev, *Acc. Chem. Res.*, 1979, **12**, 1; (*b*) M. Chorev and M. Goodman, *Acc. Chem. Res.*, 1993, **26**, 266; (*c*) M. Chorev and M. Goodman, *Trends Biotechnol.*, 1995, **13**, 438.

4 (*a*) M. M. Shemyakin, Yu. A. Ovchinnikov, V. T. Ivanov and I. D. Ryabova, *Experientia*, 1967, **23**, 326; (*b*) C. F. Hayward and J. S. Morley, in *Peptides 1974. Proceedings of the 13th European Peptide Symposium*, Israel; ed. Y. Wolman, Wiley, New York and Israel Universities, Jerusalem, 1975, p. 287; (*c*) F. E. DeBons and G. M. Loudon, *J. Org. Chem.*, 1980, **45**, 1703; (*d*) P. Moutevelis-Minakakis and I. J. Photaki, *J. Chem. Soc., Perkin Trans. 1*, 1985, **17**, 2277; (*e*) A. R. Katritzky, L. Urogdi and A. Mayence, *J. Org. Chem.*, 1990, **55**, 2206; (*f*) M. Zhao, H. K. Kleinman and M. Mokotoff, *J. Pept. Res.*, 1997, **49**, 240; (*g*) M. D. Fletcher and M. M. Campbell, *Chem. Rev.*, 1998, **98**, 763; (*h*) Y. Han, C. Giragossian, D. F. Mierke and M. Chorev, *J. Org. Chem.*, 2002, **67**, 5085.

5 Y. Nishimura, in *Studies in Natural Products Chemistry*, ed. Atta-ur-Rahman, Elsevier, Amsterdam, 1995, Vol. 16, p. 75.

6 (*a*) J. Rudinger, in *Drug Design*, ed. E. J. Ariens, Academic, New York, 1971, Vol. II, p. 319; (*b*) J. F. Hernandez, J. M. Soleihac, B. P. Roques and M. C. Fournie-Zaluski, *J. Med. Chem.*, 1988, **31**, 1825; (*c*) Y. Nishimura, E. Shitara, H. Adachi, M. Toyoshima, M. Nakajima, Y. Okami and T. Takeuchi, *J. Org. Chem.*, 2000, **65**, 2; (*d*) E. R. Lepper, S. W. Ng, M. Gutschow, M. Weiss, S. Hauschildt, T. K. Hecker, F. A. Luzzio, K. Eger and W. D. Figg, *J. Med. Chem.*, 2004, **47**, 2219.
7 For details on the use of chiral phosphoric acids as catalysts see the following reviews: (*a*) T. Akiyama, J. Itoh and K. Fuchibe, *Adv. Synth. Catal.*, 2006, **348**, 999; (*b*) S. J. Connon, *Angew. Chem.*, 2006, **118**, 4013; S. J. Connon, *Angew. Chem., Int. Ed.*, 2006, **45**, 3909.
8 For the selective deprotection of BOC and phthalimide groups see: T. W. Greene and P. G. M. Wuts, in *Protective Groups in Organic Synthesis*, Wiley: New York, 1999; 3rd edn..
9 Very limited accounts of such additions are in the chemical literature. For an intramolecular addition of an imide to an imine see: (*a*) M. Yamato, J. Horiuchi and Y. Takeuchi, *Chem. Pharm. Bull.*, 1981, **29**, 3124. For an example involving the addition of phthalimides to a C=N bond in a 2*H*-azirine see: (*b*) F. Palacios, A. M. Ochoa de Retana and J. M. Alonso, *J. Org. Chem.*, 2005, **70**, 8895.
10 CCDC 648156 contains the supplementary crystallographic data for this paper. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b709276h.