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Discovery and application of iminotriphenylphosphorane as a formal aromatic primary amine protecting group

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This letter is dedicated to all the many talented chemists who have sadly lost employment at AstraZeneca and are forced to move on to other career paths.

Keywords:
Iminotriphenylphosphorane
Primary amine protecting group
Regioselective preparation of triazoles and benzotriazoles

ABSTRACT

During our efforts to selectively synthesise *N*-arylated benzotriazole fragments, we developed a new primary aromatic amine protecting group strategy showing significant advantages over recognised protecting groups.

During a recent programme, we identified the novel fragment, 3-(1*H*-benzotriazol-1-yl)pyrazin-2-amine (**1**, Table 1), as a key substructure to acquire. Our first trials using copper-catalysed[1] and base-promoted S_NAr conditions afforded very poor isolated yields with the problems of regioselectivity (Table 1, entries 1–2). To improve yields, we turned our attention to acid-catalysed conditions and managed to develop an efficient and novel regioselective synthesis of *N*-1-linked benzotriazole 2-aminopyrazines under solvent-free conditions.[2] These conditions, although very high yielding, were determined to be unsafe for large-scale operation by DSC (differential scanning calorimetry).[3] Simple dilution of the reaction mixture with pentan-2-ol offered enough of an energy sink to make this process operable on a large-scale (Table 1, entry 4). While this process was almost entirely regioselective in the case of benzotriazole and 4-substituted benzotriazoles affording moderate to excellent yields of A (Table 1, entries 3–5), the process was not applicable for the synthesis of C-5 or C-6 substituted benzotriazoles leading to inseparable mixtures (Table 1, entry 7). Therefore, we needed to develop another strategy (Scheme 1).

To attain our targets with total regioselective control, we focused on constructing the benzotriazole ring from selectively arylated 1,2-diaminobenzene fragments (**7**)[4] with the regiochemistry fixed at the Buchwald-Hartwig amination step with the appropriate substituted 2-nitroanilines (**8**).[5] In order to carry out this approach we required to protect the C-2–NH_2 group of the readily-available 2-amino-3-chloropyrazine building block at the start of the sequence and the protecting group[6] would need to be stable to basic conditions, hydrogenation, nitrosylation and preferably, be easily removed at the end of the sequence without affecting the R groups (Scheme 1).

Inspection of the literature revealed three recognised aromatic amine protecting groups[6] in: di(Boc) (Table 2, entry 1);[7] 2,5-dimethylpyrrole (Table 2, entry 2);[8] and the very labile STABASE group (tetramethyldisliylazacyclopentane) that was excluded.[7,9] While these protecting groups have been extensively used in the past, even in our own laboratories, they can each have compatibility issues with certain chemistries and functionalities (Table 2). Herein, we communicate, to our knowledge, the first successful application of the iminotriphenylphoshporane as a formal aromatic primary amine protecting group[11] in the regioselective preparation of C3-substituted benzotriazole aminopyrazine fragments, demonstrating its thermal stability and orthogonality to the Boc group.

We decided, perhaps courageously in the absence of any real stability data,[10] to employ TPP protection with the knowledge that: (i) the –$N(Boc)_2$ group cleaves readily to –NHBoc during the

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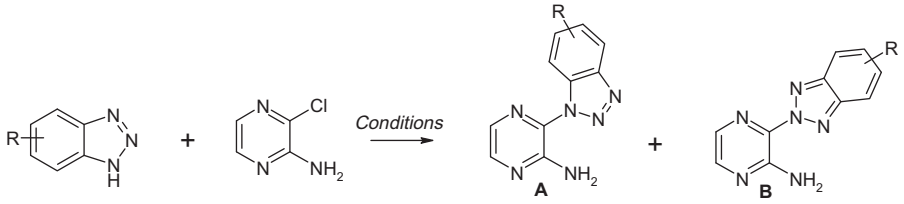
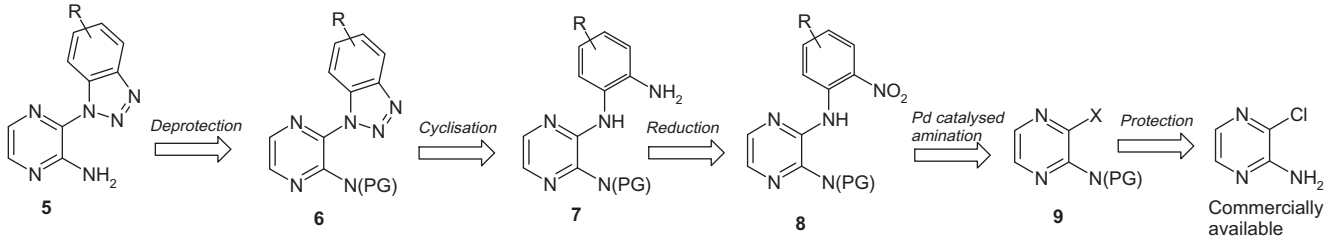
Table 1
Results obtained for the displacement of 2-amino-3-chloropyrazine with a substituted benzotriazoles under differenct conditions



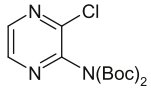
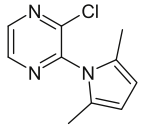
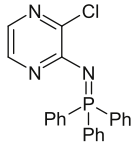
Entry	Compd	R	Conditions	Ratio (A/B)	Isolated yield (%)
1	**1**	H	CuI, TBAF, DMF, 140 °C, 16 h	80/20	14
2	**1**	H	CsF, DMSO, 120 °C, 16 h	80/20	34
3	**1**	H	Solvent-free, 140 °C, 1 h	100/0	95
4	**1**	H	Pentan-2-ol (3 vols), reflux, 16 h	100/0	82
5	**2**	4-CH_3	Solvent-free, 150 °C, 1 h	100/0	52
6	**3**	4-F	Solvent-free, 140 °C, 5 h	80[a]/20	11
7	**4**	5-CH_3	Melt conditions	100[b]/0	65

[a] Separable 70/30 mixture of C-4 and C-8–F benzotriazole isomers.
[b] Inseparable 1:1 mixture of C-5 and C-6 methylbenzotriazole isomers obtained as determined by ^{1}H NMR.



Scheme 1. Retrosynthetic analysis of target **5** (PG = protecting group, X = suitable leaving group (i.e., Cl/Br/I).

Table 2
Table showing a comparison of the common protecting groups employed for aromatic amines

Entry	Protecting group	Compd	Protection condtions	Deprotection conditions	Comments
1		**10**	Excess $(Boc)_2O$, DMAP, 50 °C, 90%	TFA, 0 °C to rt	Easy to add and remove Unstable under mildly basic conditions and to weak nucleophiles
2		**11**	Hexane-2,5-ketone, toluene, cat. TsOH, 16 h, 94%	Excess $NH_2OH{\cdot}HCl$, EtOH, H_2O, reflux, 3 d	Very stable under strongly basic conditions Very difficult to complete the deprotection and issues with hydrolysis-prone groups (e.g., even tertiary amides)
3		**12**	TPP, C_2Cl_6, TEA, toluene, 80 °C, 2 h, 92% or TPP, Cl_3CCN, toluene, 90 °C, 16 h, 92%	AcOH–H_2O (4/1), 80 °C or 2 N HCl, MeOH, 50 °C	Stable to strongly basic and thermal conditions Easy to remove with high selectivity and orthogonality

Buchwald-Hartwig amination step leading to selectivity issues and poor yields; and (ii) the 2,5-dimethylpyrrole group is known to be difficult to remove at the end of the sequence. To our satisfaction, the TPP group was stable to each step and finally easily removed by hydrolysis. After installation of the TPP group under basic conditions (Ph_3P, C_2Cl_6, TEA, toluene, 80 °C, 2 h)[11] or acidic conditions (Ph_3P, Cl_3CCN, toluene, −15 to 80 °C, 16 h), **12** was obtained in excellent yields as the free base or hydrochloride salt, respectively. The Buchwald-Hartwig step with substituted 2-nitroanilines[5] (**13**) worked efficiently affording isolated yields of **14** consistently above 60 %. We postulated that the TPP group would actually sit orthogonally to the plane of the pyrazine ring, leaving the C-3–Cl position relatively unhindered for the approach of the $(L)_nPd$ (0) species and this was confirmed by X-ray diffraction studies (Fig. 1). We also cannot exclude the possibility that the C2-N=PPh_3 group could act as a transient ligand[12] itself explaining the high yields for the amination step. Hydrogenation of **14** afforded the *ortho*-diamine intermediates **15** in good isolated yields. Finally, ring closure[4] followed by hydrolysis[13] of the C-2–N=PPh_3 group gave our desired fragments (**17**) in satisfactory to excellent overall yields (Scheme 2).

After having successfully employed the TPP protecting group to synthesise our benzotriazole fragments with total regiocontrol, we turned our attention to its suitability for the regioselective synthe-

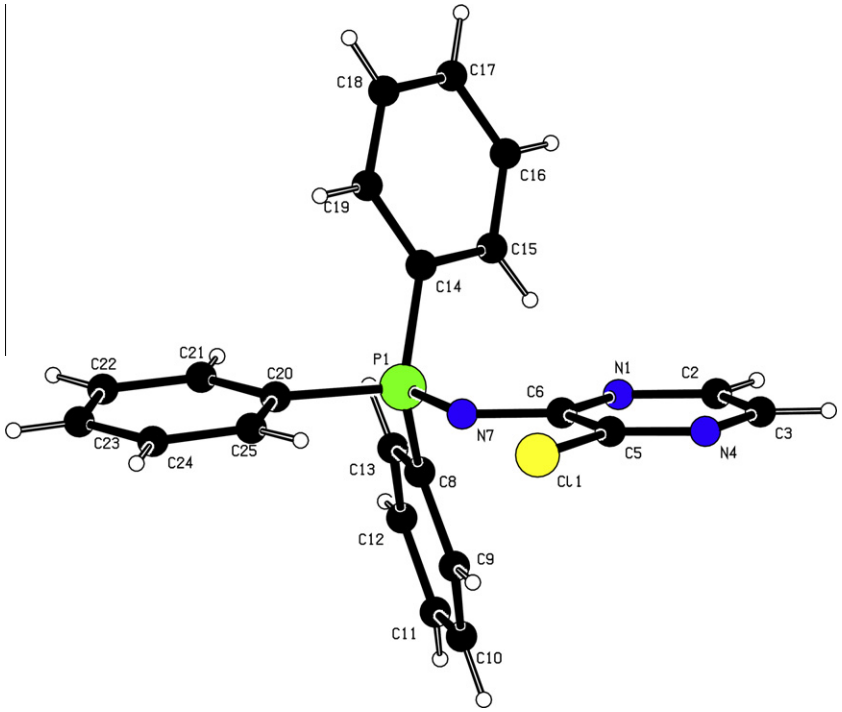
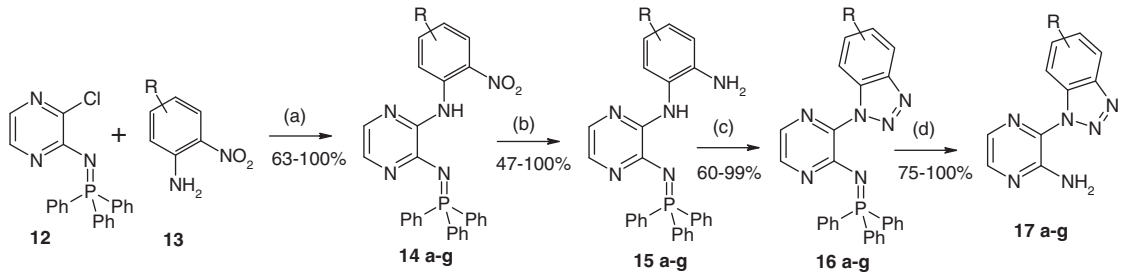
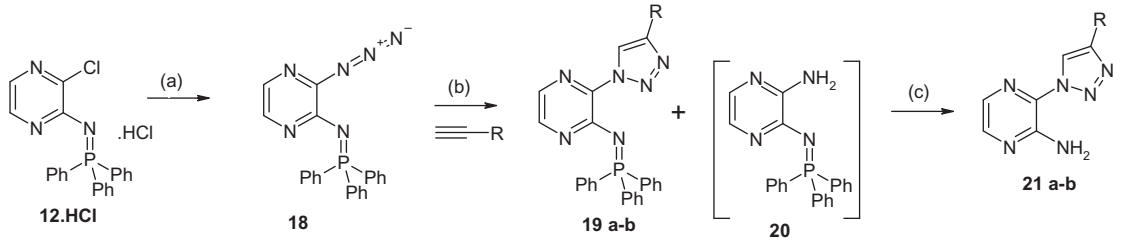


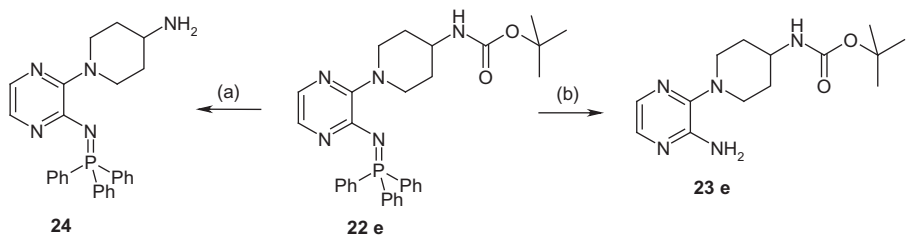
Figure 1. X-ray analysis of **12**. The C-2–N=PPh_3 group is sitting below the C-3–Cl bond, orthogonal to the plane of the pyrazine ring.



Scheme 2. Regioselective preparation of *N*-1-arylated benzotriazole fragments. Reagents and conditions: (a) $Pd(OAc)_2$, xantphos, Cs_2CO_3, toluene, 100 °C, 16 h; (b) H_2, Pd-C, EtOAc, rt, 16 h or H_2 (15 psi), PtO_2, EtOAc–EtOH, rt; (c) isoamylnitrite, AcOH, rt; (d) 2 N HCl, MeOH, 80 °C, 2 h, 75%-quant (where R is: (a) 4-OCH_3; (b) 5-OCH_3; (c) 6-OCH_3; (d) 5-CH_3; (e) 6-CH_3; (f) 5-F; (g) 6-F).

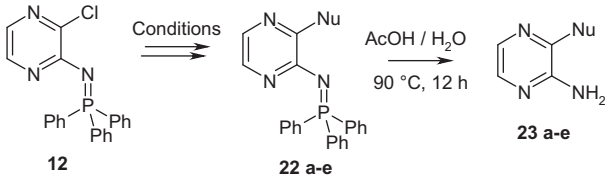


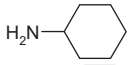
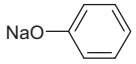
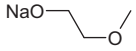
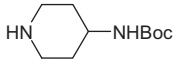
Scheme 3. Regioselective preparation of *N*-1-arylated triazole fragments. Reagents and conditions: (a) NaN_3, DMSO, 90 °C, 16 h, 96%; (b) CuI, toluene, 50 °C, 16 h, R = Ph (**19a**, 55%) R = *t*-Bu (**19b**, 45%); (c) 2 N HCl (aq), MeOH, 80 °C, 2 h R = Ph (**21a**, 74%), R = *t*-Bu (**21b**, 85%).



Scheme 4. Orthogonality of the TPP to the Boc group. Reagents and conditions: (a) TFA–DCM (80/20), 0 °C-rt, 78%; (b) AcOH–H_2O (80/20), 90 °C, 5 h, 89%.

Table 3
Results obtained from nucelophilic substitution of **12** with a variety of nucleophiles



Entry	Compd	Nucelophile	Conditions	Conversion/isolated yield (%)
1	**22a**		Neat, 160 °C, 5 h	100/87
2	**22b**		Neat, 160 °C, 5 h Neat, 170 °C, 16 h	25/NA 88/65
3	**22c**		5 equiv, NMP, 130 °C, 16 h 5 equiv, NMP, 160 °C, 16 h	5/NA 95/52
4	**22d**		5 equiv 130 °C, 2 h	100/87
5	**22e**		5 equiv, NMP, 130 °C, 16 h	89/74

sis of triazoles using 'Click' chemistry (Scheme 3).[14] The added hydrocarbon weight of the TPP group permitted the safe preparation and manipulation of the C-3 azide intermediate **18**. In the absence of the TPP group, the intermediate azide has 62% nitrogen content and could be classed as a potential explosive.[15] The subsequent 'Click' reaction proceeded with high regiocontrol as expected affording satisfactory yields of triazole products (**19a**, **19b**) with the reduced C-3–NH_2 side product (**20**).[16]

Finally, although S_NAr of C-2-amino-3-chloropyrazine is well known in the absence of any protecting group, we were curious to test the thermal stability of this group with the knowledge that the Boc group undergoes readily thermolysis above 150 °C.[17] We prepared a small library to illustrate the thermal stability of the C-2–N=PPh_3 group to a large excess of oxygen- and nitrogen-based nucleophiles at very high temperatures for prolonged periods of time (Table 3). Compound **22e** allowed us to illustrate nicely how Boc and TPP can be deprotected selectively and are stable to each other's deprotection conditions. This interesting observation could be exploited further by using polymer-supported triphenylphosphine in an anchoring strategy (Scheme 4).

In conclusion, we have discovered a novel aromatic primary amine protecting group and demonstrated its application to the regioselective synthesis of 2-amino-3-*N*-1-linked triazole and benzotriazole pyrazine fragments on multi-gram quantities. We have also demonstrated the thermal stability and orthogonality of the TPP to the Boc group and are currently looking at extending the scope and application of this protecting group system.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.106.

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3. DSC testing of the melt reaction between 2-amino-3-chloropyrazine and 1,2,3-1*H*-benzotriazole gave the following results: A strong, uncontrollable exotherm was observed at the onset of the reaction taking the temperature from 130 to 192 °C on a 10 g scale over 14 min. The exothermic behaviour did appear to subside slightly at this point but then accelerated in rate with the test having to be terminated before damaging temperature/pressure occurred. Maximum rates of temperature rise (30 K/s) and pressure (20 bar/s) were recorded at approximately 270 °C. Residual pressure was approximately 5.1 bar. Significant gas evolution also appeared to occur from 149 °C.
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