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Triphenylphosphonium perchlorate as an efficient catalyst for mono- and bis-intramolecular imino Diels–Alder reactions: synthesis of tetrahydrochromanoquinolines

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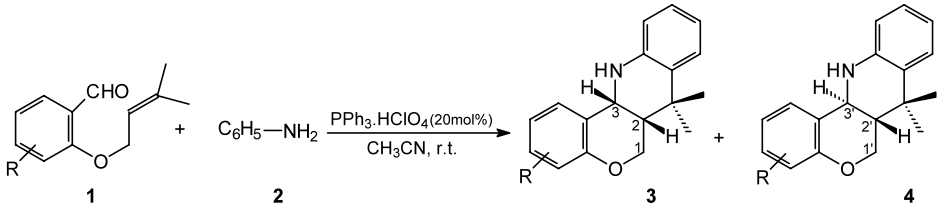
Abstract—Triphenylphosphonium perchlorate (TPP) is found to be an efficient catalyst for the mono- and bis-intramolecular imino Diels–Alder (IMIDA) reaction of aldimines derived from aromatic amines and *O*-allyl derivatives of salicylaldehydes to afford the corresponding tetrahydrochromano[4,3-*b*]quinolines in excellent yields and short reaction times under mild conditions.

Tetrahydroquinoline derivatives are found to exhibit a wide range of biological activities,[1] including psychotropic, anti-allergic, anti-inflammatory and estrogenic behaviour. The [4+2] Diels–Alder reaction between *N*-arylimines and electron-rich dienophiles is a powerful synthetic tool for constructing *N*-containing six-membered heterocyclic compounds as well as in the synthesis of natural products[2] including tetrahydroquinoline derivatives.[3] In addition, intramolecular imino Diels–Alder reactions provide multiple opportunities for the stereoselective construction of tetrahydroquinolines. The inter- and intramolecular imino Diels–Alder reaction of imines with electron rich dienophiles has been catalyzed by Lewis acids such as $BF_3{\cdot}Et_2O$,[3b,4] $InCl_3$,[5] transition metal carbonyls,[6] lanthanide triflate[7] as well as Brønsted acids such as TFA[8] and *p*-TsOH.[9] It has previously been reported that for the intramolecular imino Diels–Alder reaction of aldimines derived from aromatic amines and *O*-allyl derivatives of salicylaldehyde, $Yb(OTf)_3$, TFA,[10] $BiCl_3$,[11] $LiClO_4$[12] are effective catalysts. However, some of these reagents suffer from one or other disadvantages such as strongly acidic nature, nucleophilic character (ClO_4^-), expense, long reaction times, and low yields. Moreover, many Lewis acids are either decomposed or deactivated due to the formation of water during imine formation. Triphenylphosphonium perchlorate (TPP) is inexpensive, readily available and found to retain its activity even in the presence of amines, water and other active functional groups such as NO_2, COOH, CN present in the substrates.

In the imino Diels–Alder reactions, it is necessary to activate the imine double bond. This is due to the low electrophilicity of the imines as compared to the corresponding carbonyl compounds. The activation of the imine can be achieved by coordination of triphenylphosphonium perchlorate ($PPh_3{\cdot}HClO_4$) at the imine nitrogen. Recent progress includes the use of TPP as the catalyst for imino Diels–Alder reactions[13] and



Scheme 1.

Keywords: triphenylphosphonium perchlorate; mono- and bis-IMIDA; hetero-polycyclic systems.
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one-pot reactions using imines formed in situ from benzaldehydes and amines.[14] In continuation of our interest in catalytic applications of TPP,[15] we herein describe another remarkable catalytic activity of TPP in the synthesis of tetrahydrochromano[4,3-*b*]quinolines from aromatic amines and *O*-allyl derivatives of salicylaldehydes via the mono- and bis-intramolecular [4+2] cyclization of imines in acetonitrile at room temperature in excellent yields.

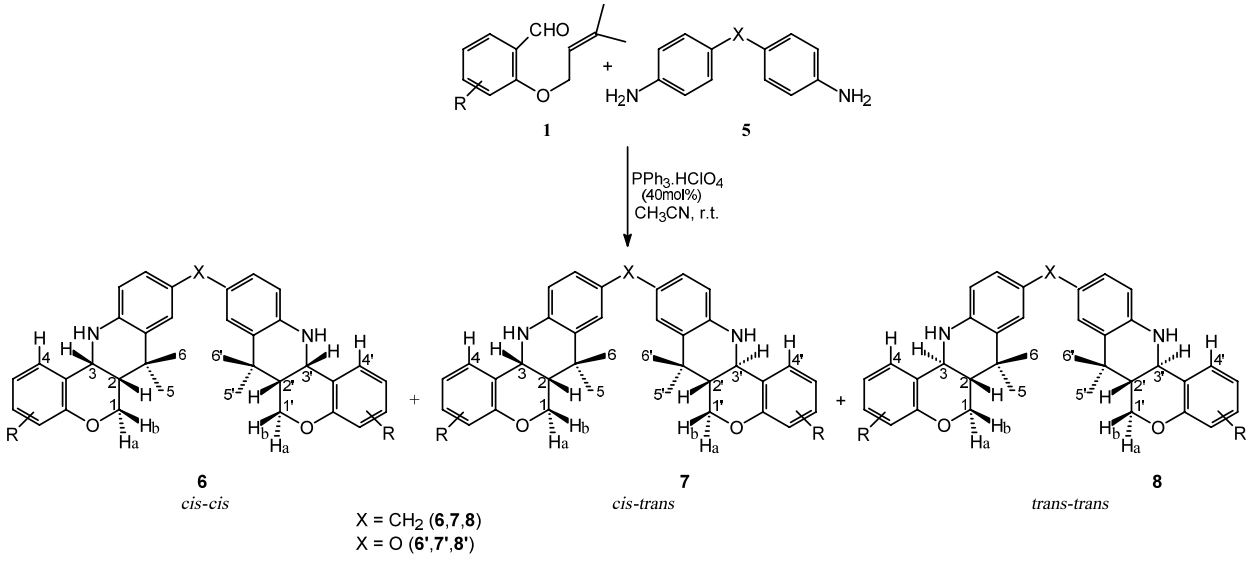
In the presence of 20 mol% TPP, arylimine derived in situ from aniline and the *O*-prenyl derivative of salicylaldehyde over anhydrous Na_2SO_4 in acetonitrile at room temperature gave tetrahydrochromanoquinolines in 82–94% yield as a mixture of diastereoisomers **3** and **4** (Scheme 1). In all cases, the products were obtained as a mixture of *cis* and *trans* isomers in a 1:1 ratio, determined from the ^{1}H NMR spectrum of the crude product. These isomers were isolated by column chromatography on silica gel. Several other aromatic imines underwent smooth cycloaddition to give the corresponding tetrahydrochromanoquinolines in good yields (Table 1). The *cis*- and *trans*-stereochemistry of the products was assigned on the basis of coupling constants of the protons in the ^{1}H NMR spectra and also by direct comparison with literature data wherever available.[10,11]

Similarly, the reaction of imines derived in situ from *O*-allyl salicylaldehydes and 4,4′-methylenedianiline or 4,4′-oxadianiline **5** over anhydrous Na_2SO_4 in acetonitrile in the presence of 40 mol% TPP underwent intramolecular bis-cyclization to give the corresponding bis-4,4′-methylene or 4,4′-oxatetrahydrochromano[4,3-*b*]quinolines as a mixture of three isomers **6**, **7** and **8** or **6′**, **7′** and **8′** in good yields in nearly a 1:1:1 ratio (Scheme 2). The product ratio was determined by examination of the ^{1}H NMR spectrum of the crude product mixture. These isomers were successfully isolated by column chromatography on silica gel (100–200 mesh). Similarly, various substituted *N*-arylimines were examined and the results are summarized in Table 2.

Table 1. TPP catalyzed synthesis of tetrahydrochromano[4,3-*b*]quinolines via IMIDA[a]

Entry	Ar	R	Time (min)	Yield (%)[b]		Overall yield (%) (**3**+**4**)
				3	**4**	
a	C_6H_5	H	15	49	45	94
b	C_6H_5	3-CH_3O	25	43	46	89
c	2-CH_3-C_6H_4	H	20	40	47	87
d	4-CH_3O-C_6H_4	H	30	42	50	92
e	4-Br-C_6H_4	H	20	41	47	88
f	4-O_2N-C_6H_4	H	15	40	45	85
g	4-HOOC-C_6H_4	H	30	42	45	87
h	4-NC-C_6H_4	H	35	44	38	82
i	C_6H_5	5-Cl	20	48	43	91
j	1-Naphthyl	H	40	38	46	84

[a] All the products were characterized by IR, ^{1}H, ^{13}C NMR and mass spectroscopy and by comparison with reported data.
[b] Yield refers to the 1:1 diastereoisomers of products **3** and **4** isolated in pure form by column chromatography.



Scheme 2.

Table 2. TPP catalyzed synthesis of *bis*-4,4′-methylene or 4,4′-oxatetrahydrochromano-[4,3-*b*]quinolines via IMIDA[a]

Entry	X	R	Time (min)	Yield (%)[b] **6 7 8** or **6′ 7′ 8′**			Overall yield (%)
a	CH_2	H	35	30	28	34	92 (**6**+**7**+**8**)
b	CH_2	3-CH_3O	45	29	25	32	86 (**6**+**7**+**8**)
c	O	H	40	31	33	25	89 (**6′**+**7′**+**8′**)
d	O	5-Cl	30	25	31	26	82 (**6′**+**7′**+**8′**)

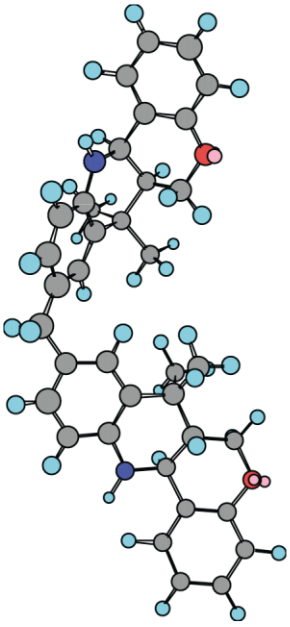
[a] All the products were characterized by IR, ^1H, ^{13}C NMR and mass spectroscopy.
[b] Yield refers to the 1:1:1 mixture of diastereoisomers of products **6**, **7** and **8** isolated in pure form by column chromatography.

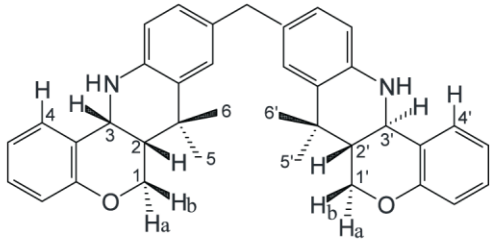
The stereochemistry of each isomer was assigned by ^1H NMR and NOE studies. In the *cis–trans* isomer **7**, the coupling constant between H3 (δ 4.55, d) and H2 (δ 2.00, dt) had a small J value ($J_{2-3}=2.4$ Hz). This indicates *cis*-fusion at the ring junction, which was further confirmed by a strong NOE between them. Also, the coupling constant between H3′ (δ 4.41, d) and H2′ (δ 2.08, td) had a large J value ($J_{2'-3'}=10.8$ Hz). This indicates *trans* fusion at the ring junction, which was further confirmed by the absence of an NOE between them (Fig. 1).

We found that the mono- and bis-intramolecular cyclization can be carried out very conveniently as a one-pot reaction starting from the *O*-allyl salicylaldehydes and arylamines without isolation of the intermediate imines. Both diimine formation and bis-cyclization could be achieved in one sequential transformation. This would be a highly desirable method for the preparation of hetero-polycyclic systems, in which isolation and purification of intermediates could be avoided.[16]

It can be concluded that triphenylphosphonium perchlorate (TPP) is an efficient catalyst for both mono- and bis-cyclization of aromatic amines with *O*-allyl salicylaldehyde derivatives in a one-pot reaction to afford tetrahydrochromanoquinolines. In addition to its efficiency, simplicity and mild reaction conditions, the catalyst is very cheap and only a small amount (20 or 40 mol%) is needed. This method provides high yields of products in short reaction times, making it a useful process for the synthesis of hetero-polycyclic systems. Further synthetic application of these reactions is now in progress.

General experimental procedure: 20 mol% TPP (0.6 mmol, 206 mg) was added to a mixture of *O*-allyl salicylaldehyde **1a** (3 mmol, 570 mg. For bis-cyclization 2 equiv. of *O*-allyl salicylaldehyde and 40 mol% TPP were used), arylamine **2a** (1 equiv. 279 mg) and anhydrous Na_2SO_4 in acetonitrile (20 mL). The reaction mixture was stirred at room temperature for an appropriate time. On completion, as indicated by TLC, the mixture was quenched with water and extracted with ethyl acetate, the organic layer was washed with brine and dried over Na_2SO_4. The solvent was evaporated in vacuo and the crude product was chromatographed on silica gel (EtOAc:hexane mixture) to afford analytically pure diastereoisomers **3** and **4** or **6**, **7** and **8** in 82–94% yields.





H-H interaction in NOE spectra (in $CDCl_3$)

H2-H1b; H2-H3;
H3-H2; H3-H1b; H3-H4 and
H2'-H1'b; H2'-H6'

Figure 1. H–H interactions observed in the NOE spectra and the MM2-energy minimized structure of **7a**. Non-systematic numbering.

Representative spectral data of the products. Compound **3f**: yellow colored solid, mp: 184–186°C (uncorrected); IR (KBr) 3363 (NH), 3081, 2969, 2936, 2878, 1606, 1559, 1522, 1467, 1327, 1226, 1124, 1018, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.53 (s, 3H), 2.10 (dt, 1H, H-2, $J=12.0$, 2.3 Hz), 3.57 (t, 1H, H-1a, $J=12.0$ Hz), 4.25 (dd, 1H, H-1b, $J=10.9$, 2.3 Hz), 4.66 (d, 1H, H-3, $J=3.5$ Hz), 6.36 (d, 1H, $J=8.6$ Hz), 6.88 (d, 1H, $J=8.6$ Hz), 6.95–7.02 (m, 2H), 7.25–7.28 (m, 1H), 7.91 (dd, 1H, $J=9.2$, 2.3 Hz), 8.09 (d, 1H, $J=6.3$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$, proton decoupled) δ 25.3, 32.9, 33.7, 39.7, 46.4, 63.1, 112.5, 117.3, 121.0, 122.1, 122.9, 124.7, 125.9, 129.4, 130.3, 138.2, 146.3, 153.9; MS (m/z) 310 (M^+).

6a: yellow colored solid, mp: 206–208°C (uncorrected); IR (KBr) 3399 (NH), 3022, 2966, 2917, 1612, 1586, 1504, 1294, 1232, 1019, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (s, 6H), 1.33 (s, 6H), 1.92 (dt, 2H, H-2, $J=12.2$, 3.9 Hz), 3.69 (s, 4H), 3.79 (t, 2H, H-1a, $J=10.7$ Hz), 4.17 (dd, 2H, H-1b, $J=10.7$, 2.9 Hz), 4.47 (d, 2H, H-3, $J=2.4$ Hz), 6.27 (d, 2H, $J=8.3$ Hz), 6.66–7.48 (m, 12H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$, proton decoupled) δ 25.7, 33.4, 34.1, 40.8, 46.0, 63.7, 65.4, 113.6, 116.7, 120.3, 124.0, 126.1, 126.8, 127.6, 128.3, 129.3, 129.4, 138.5, 153.9; MS (m/z) 542 (M^+).

7a: yellow colored solid, mp: 108–110°C (uncorrected); IR (KBr) 3389 (NH), 3029, 2962, 2928, 2871, 1610, 1585, 1493, 1225, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 3H), 1.36 (s, 3H), 1.41 (s, 3H), 1.44 (s, 3H), 2.00 (dt, 1H, H-2, $J=8.8$, 3.2 Hz), 2.08 (td, 1H, H-2′, $J=11.6$, 3.2 Hz), 3.74 (s, 2H, -CH_2-), 3.83 (t, 1H, H-1a, $J=11.0$ Hz), 3.91 (t, 1H, H-1′a, $J=11.1$ Hz), 4.24 (dd, 1H, H-1b, $J=10.8$, 2.8 Hz), 4.41 (d, 1H, H-3′, $J=10.8$ Hz), 4.48 (dd, 1H, H-1′b, $J=10.8$, 2.8 Hz), 4.55 (d, 1H, H-3, $J=2.4$ Hz), 6.34 (d, 1H, $J=8.1$ Hz), 6.62 (d, 1H, $J=8.1$ Hz), 6.86–7.34 (m, 12H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$, proton decoupled) δ 27.3, 28.1, 29.7, 34.1, 34.5, 34.7, 40.6, 40.8, 44.1, 46.1, 47.8, 63.7, 65.6, 113.5, 116.4, 116.8, 117.1, 120.3, 120.8, 123.8, 124.0, 125.7, 126.1, 126.9, 127.3, 127.4, 127.7, 128.5, 129.4, 129.5, 130.2, 131.5, 132.3, 138.6, 141.0, 153.9, 154.2; MS (m/z) 542 (M^+).

8a: yellow colored solid, mp: 121–123°C (uncorrected); IR (KBr) 3385 (NH), 3023, 2964, 2925, 1617, 1581, 1510, 1295, 1237, 1016, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 6H), 1.37 (s, 6H), 2.00 (dt, 2H, H-3 and H-3′, $J=11.2$, 2.9 Hz), 3.76 (s, 2H, -CH_2-), 3.86 (t, 2H, H-1a and 1′a, $J=11.2$ Hz), 4.33 (d, 2H, H-3 and 3′, $J=10.7$), 4.40 (dd, 2H, H-1b and 1′b, $J=10.7$, 2.9 Hz), 6.55 (d, 2H, $J=8.3$ Hz), 6.77–6.82 (m, 2H), 6.91 (t, 2H, $J=7.3$), 7.03 (s, 2H), 7.12 (t, 2H, $J=7.3$ Hz), 7.18 (s, 2H), 7.27 (d, 2H, $J=7.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$, proton decoupled) δ 27.3, 28.0, 34.5, 40.7, 44.1, 47.8, 65.6, 116.4, 117.0, 120.8, 123.8, 125.7, 127.3, 127.4, 128.5, 131.5, 132.0, 141.0, 154.1; MS (m/z) 542 (M^+).

7′c: yellow colored solid, mp: 115–117°C (uncorrected); IR (KBr) 3398 (NH), 3066, 2973, 2923, 1735, 1608, 1469, 1268, 1218, 1098, 945, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.29 (s, 3H), 1.34 (s, 3H), 1.37 (s, 3H), 1.92 (dt, 1H, H-2, $J=12.2$, 3.4 Hz), 2.00 (td, 1H, H-2′, $J=11.2$, 2.9 Hz), 3.78 (t, 1H, H-1a, $J=12.2$ Hz), 3.86 (t, 2H, H-1′a, $J=11.2$ Hz), 4.17 (dd, 1H, H-1b, $J=10.7$, 2.9 Hz), 4.33 (d, 1H, H-3′, $J=11.2$ Hz), 4.41 (dd, 1H, H-1′b, $J=10.7$, 2.9 Hz), 4.48 (d, 1H, H-3, $J=3.7$ Hz), 6.27 (d, 1H, $J=7.8$ Hz), 6.50–7.23 (m, 12H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$, proton decoupled) δ 25.7, 27.3, 28.0, 33.4, 34.1, 34.5, 40.8, 44.1, 46.1, 47.8, 63.7, 65.6, 113.3, 113.6, 116.4, 116.7, 117.0, 120.3, 120.8, 123.8, 124.0, 125.7, 126.1, 126.9, 127.3, 127.4, 127.6, 128.4, 129.5, 130.2, 131.5, 132.3, 138.5, 140.9, 153.9, 154.2; MS (m/z) 544 (M^+).

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