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# Stable Preformed Chiral Palladium Catalysts for the One-Pot Asymmetric Reductive Amination of Ketones

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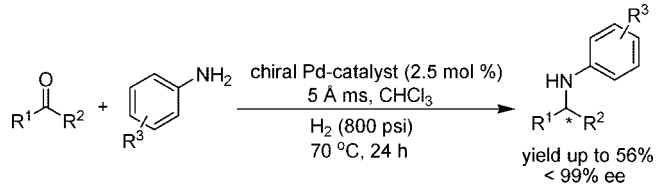
## ABSTRACT




$R^1$ = alkyl or aryl; $R^2$ = alkyl; $R^3$ = donating and electro-drawing groups

**The application of air stable preformed [(*R*)-BINAP]$PdBr_2$, [(*S*)-BINAP]$PdBr_2$, [(*R*)-Tol-BINAP]$PdBr_2$, and [(*S*,*S*)-CHIRAPHOS]$PdBr_2$ complexes in the one-pot asymmetric reductive amination of various carbonyl compounds, leading to chiral amines in very good yields with high enantioselectivities (<99% ee), is reported.**

Chiral amines are key compounds in pharmaceutical, agrochemical, and materials industries.[1] Lower aliphatic amines are used as organic intermediates for the synthesis of bactericides, drugs, herbicides, rubber accelerators, corrosion inhibitors, and surface-active agents.[2,3] Their formation drives the development of efficient methods as catalytic asymmetric reactions. Some of the past studies in this field have focused on the enantioselective reduction of a C−N double bond, using a variety of chiral Pd, Ti, Rh, and Ir complexes.[4,5] Recently, the direct reductive amination (DRA) of ketones/aldehydes with amines is an elegant and powerful tool used for the syntheses of structurally diverse amines in modern organic chemistry; the advantage of this reaction is that there is no need to isolate intermediate imines.[6] A few preliminary studies on selected asymmetric reductive aminations of

(1) (a) Main, B. G.; Tucker, H. In *Medicinal Chemistry*, 2nd ed.; Genellin, C. R., Roberts, S. M., Eds.; Academic Press: New York, 1993; p187. (b) Gröger, H.; May, O.; Werner, H.; Menzel, A.; Altenbuchner, J. *Org. Process Res. Dev.* **2006**, *10*, 666. (c) Chen, B.; Dingerdissen, U.; Krauter, J. G. E.; Rotgerink, G. J. L.; Möbus, K.; Ostgard, D. J.; Panster, P.; Riermeier, T. H.; Seebald, S.; Tacke, T.; Trauthwein, H. *Appl. Catal., A* **2005**, *280*, 17.

(2) (a) Merla, B.; Risch, N. *Synthesis* **2002**, 1365. (b) Henkel, T.; Brunni, R. M.; Mueller, H.; Reichert, F. *Angew. Chem., Int. Ed. Engl.* **1993**, *38*, 643. (c) Bhanushali, M.; Nandurkar, N. S.; Bhor, M. D.; Bhanage, B. M. *Tetrahedron Lett.* **2007**, *48*, 1273.

(3) Sharp, D. B. In *Herbicides: Chemistry, Degradation and Mode of Action*; Kearney, P. C., Kaufman, D. D., Eds.; Marcel Dekker: New York, 1988; Chapter 7.

(4) For a general review of the reduction of imines, see: (a) Vilaivan, T.; Bhanthumnavin, W.; Sritana-Anant, Y. *Curr. Org. Chem.* **2005**, *9*, 1315. (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (c) Cho, B. T. *Tetrahedron* **2006**, *62*, 7621.

(5) For reduction of imines catalyzed by Ti, Ru, Rh, Ir, and Pd, see: (a) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 11703. (b) Verdaguer, X.; Lange, U. E. W.; Reding, M. T.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 6784. (c) Hanson, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 713. (d) Cheemala, M. N.; Knochel, P. *Org. Lett.* **2007**, *9*, 3089. (e) Moessner, C.; Bolm, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 7564. (f) Vargas, S.; Rubio, M.; Suárez, A.; Río, D. D.; Álvarez, E.; Pizzano, A. *Organometallics* **2006**, *25*, 961. (g) Guiu, E.; Aghmiz, M.; Diaz, Y.; Claver, C.; Meseguer, B.; Militzer, C.; Castillón, S. *Eur. J. Org. Chem.* **2006**, 627. (h) Iwadate, N.; Yoshida, K.; Imamoto, T. *Org. Lett.* **2006**, *8*, 2289. (i) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916. (j) Samec, J. S. M.; Bäckvall, J. E. *Chem.—Eur. J.* **2002**, *8*, 2955. (k) Cobley, C. J.; Henschke, J. P. *Adv. Synth. Catal.* **2003**, *345*, 195. (l) Abe, H.; Ammii, H.; Uneyama, K. *Org. Lett.* **2001**, *3*, 313.

(6) Hutchins, R. O.; Hutchins, M. K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, p 25.

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ketones, giving chiral branched amines in an enantioface-differentiating process have been reported.[7,8] Blaser et al. have presented the first example of asymmetric direct reductive amination using Ir−Xyliphos complex as catalyst.[9] In other reports, organocatalytic[10] and hydrogen transfer[11] approaches were used. Hence, there is a continuing need for convenient methods for the synthesis of chiral amines from ketones. On the other hand, chiral palladium diphosphosphine complexes have been employed as catalysts for many organic syntheses.[12] Changes in the geometry of diphosphine ligands, steric and electronic factors, may lead to drastic variations on the reactivity and stereocontrol.

In our research on the carbonylation of imines, we found an interesting competitive reduction process. Here we wish to present the novel use of preformed air stable chiral palladium catalysts in the asymmetric reductive amination of a series of alkyl, cycloaliphatic, and aromatic carbonyl compounds with aniline derivatives, using molecular sieves[13] and hydrogen pressure to synthesize chiral secondary amines. These results appear to be the first report on the application of these complexes in the one-pot reductive amination reactions of carbonyl compounds. Here we also report, the X-ray structures of [(*R*)-BINAP]$PdBr_2$ and [(*S*,*S*)-CHIRAPHOS]$PdBr_2$.

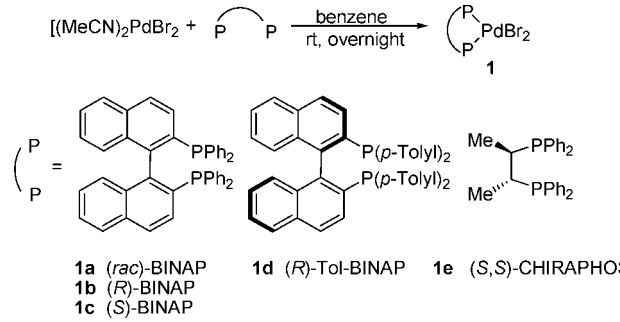
Scheme 1 illustrates the different preformed chiral (diphosphine) palladium(II) dibromide complexes employed in this study. These were prepared by the reaction of $(MeCN)_2PdBr_2$ with the corresponding diphosphine ligands in benzene.

In our initial practice, the asymmetric reductive amination of compound **2a** with **3a** was tested in the presence of the chiral palladium catalysts in $CHCl_3$ solvent at 70 °C for 24 h (Table 1). Both **1b** and **1d** are good catalysts, as they produce high enantioselectivities (76 and 77% ee respectively). The best yield is obtained when complex **1b** is used (81%). However, the reaction catalyzed by **1e,** is less active than **1b** or **1d** yielding 45% of product with 14% ee.

The X-ray structures of [(*R*)-BINAP]$PdBr_2$ (**1b**) and [(*S*,*S*)-CHIRAPHOS]$PdBr_2$ (**1e**) complexes are shown in Figures 1 and 2, respectively. Palladium has a distorted square planar geometry in both complexes. The P−Pd−P bite angle of the (*R*)-BINAP ligand (92.58(5)°) in **1b** is similar to analogous [(*R*)-BINAP]$PdCl_2$ complex (92.68(8)°).[14] The Pd−P and Pd−Br distances are 2.2499(9) and 2.4766(5) Å, respectively. On the other hand, **1e** exhibits a P−Pd−P bite angle equal to 86.05(5)°, which is shorter than that found in complex **1b**, where the Pd−P and Pd−Br distances are 2.2320(6) and 2.4737(1) Å, respectively. A larger bite angle and ligand flexibility exhibited by the ligand in complex **1b**play a crucial role during the reaction, as noted by complex **1e** being less efficient, leading to the formation of **4a** in low yield and poor stereocontrol.

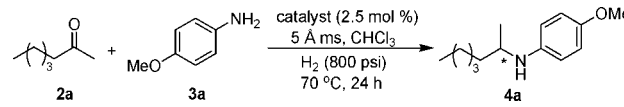
To probe the generality of catalyst **1b** or **1c**, a series of alkyl and cycloaliphatic ketones were evaluated, using *o*-, *m*- and *p*-substituents on aniline derivatives (Table 2). All reactions were carried out in chloroform under 800 psi of hydrogen pressure with 2.5 mol % of the catalyst. The results were obtained with respect to isolated yield and enantioselectivity of products, demonstrating the generality of the asymmetric reductive amination. The reactions of 2-heptanone with **3b** and **3c** gave the **4b** and **4c** in good yields

**Scheme 1.** Synthesis of Chiral Pd-Catalysts




**1a** (*rac*)-BINAP **1b** (*R*)-BINAP **1c** (*S*)-BINAP **1d** (*R*)-Tol-BINAP **1e** (*S*,*S*)-CHIRAPHOS

**Table 1.** Asymmetric Reductive Amination of **2a**[a]




**2a** **3a** **4a**

| entry | catalyst | yield[b] (%) | ee[c] (%) |
|---|---|---|---|
| 1 | **1a** | 83 | |
| 2 | **1b** | 81 | 76 |
| 3 | **1c** | 43 | 17[d] |
| 4 | **1d** | 55 | 77 |
| 5 | **1e** | 45 | 14 |

[a] Reactions were carried out with 2.5 mol % of catalyst, 1.0 mmol of 2-heptanone (**2a**), 1.5 mmol of *p*-anisidine (**3a**), 150 mg of 5 Å ms, 10 mL $CHCl_3$ and $H_2$ (800 psi) at 70 °C for 24 h. [b] Isolated yield. [c] The ee values were determined by HPLC. [d] Reaction was carried out at rt.

(7) For a review on asymmetric reductive amination, see: Tararov, V. I.; Börner, A. *Synlett* **2005**, 203.

(8) For asymmetric reductive aminations catalyzed by metal complexes, see: (a) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Börner, A. *Chem. Commun.* **2000**, 1867. (b) Chi, Y. X.; Zhou, Y. G.; Zhang, X. *J. Org. Chem.* **2003**, *68*, 4120. (c) Kadyrov, R.; Riermeier, T. H.; Dingerdissen, U.; Tararov, V.; Börner, A. *J. Org. Chem.* **2003**, *68*, 4067. (d) Salmi, Ch.; Letourneux, Y.; Brunel, J. M. *Lett. Org. Chem.* **2006**, *3*, 384. (e) Nugent, T. C.; Wakchaure, V. N.; Ghosh, A. K.; Mohanty, R. R. *Org. Lett.* **2005**, *7*, 4967. (f) Zhang, X. Asymmetric Reductive Amination of Ketones. U.S. Patent WO2004058982, 2004.

(9) Blaser, H.-U.; Buser, H.-P.; Jalett, H.-P.; Pugin, B.; Spindler, F. *Synlett* **1999**, 867.

(10) For organocatalytic reductive aminations, see: (a) Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84. (b) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424.

(11) For transfer hydrogen in reductive aminations, see: (a) Williams, G. D.; Pike, R. A.; Wade, C. E.; Will, M. *Org. Lett.* **2003**, *5*, 4227. (b) Kadyrov, R.; Riermeier, T. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5472. Reductive amination via dynamic kinetic resolution, see: (c) Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074.

(12) (a) McCarthy, M.; Guiry, P. J. *Tetrahedron* **2001**, *57*, 3809. (b) Shimizu, H.; Nagasaki, I.; Saito, T. *Tetrahedron* **2005**, *61*, 5405.

(13) Molecular sieves were used to absorb water molecules, which are generated by the condensation between the ketone and the aromatic amine.

(14) Ozawa, F.; Kubo, A.; Matsumoto, Y.; Hayashi, T.; Nishioka, E.; Yanagi, K.; Moriguchi, K. *Organometallics* **1993**, *12*, 4188.

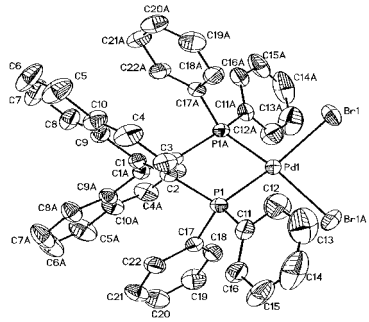


**Figure 1.** X-ray structure of [(*R*)-BINAP]PdBr$_2$ complex (**1b**). Selected bond lengths (Å) and angles (deg): Pd1−P1 2.2468(8), Pd1−P1A 2.2468(8), Pd1−Br1 2.4742(4), Pd1−Br1A 2.4742(4), P1−Pd1−P1A 92.66(4), Br1−Pd1−Br1A 93.70(2), P1−Pd1−Br1 91.12(2), P1A−Pd−Br1A 91.12(2), P1−Pd1−Br1A 157.66(2), P1A−Pd1−Br1 157.66(2).

(51−84%, entries 1−2), but the best enantioselectivity was observed when *m*-trifluoromethyl aniline (**3c**) is used (95% ee). In the case of 3-heptanone with **3d** and **3e** gave the

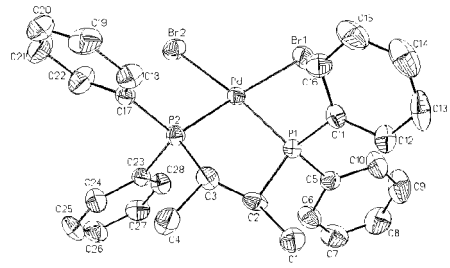
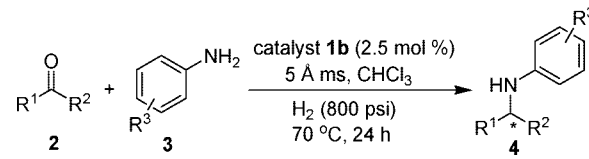
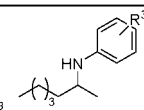
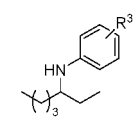
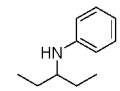
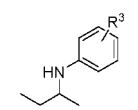
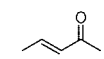
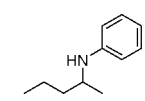
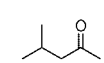
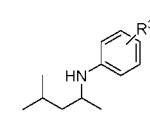
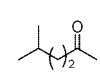
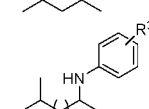
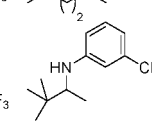
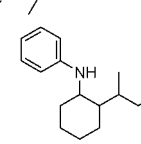
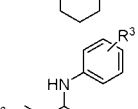


**Figure 2.** X-ray structure of [(*S*,*S*)-CHIRAPHOS]PdBr$_2$ complex (**1e**). Selected bond lengths (Å) and angles (deg): Pd−P1 2.2305(1), Pd−P2 2.2336(1), Pd−Br1 2.4704(6), Pd−Br2 2.4769(6); P1−C2 1.865(5), P2−C3 1.858(5), P1−Pd1−P2 86.05(5), Br1−Pd−Br2 94.10(2), P1−Pd−Br1 89.38(4), P2−Pd−Br2 90.67(4), P2−Pd−Br1 174.79(4), P1−Pd− Br2 174.00(4).

desired products with moderate enantioselectivities (entries 3−4, 49−59% ee). A marked stereochemical effect was observed with respect to the position of the carbonyl group of the substrate (entries 1 and 4). 2-Butanone was reductively aminated with *o*-, *m*- and *p*-aniline derivatives (**3g**−**j**) and the products were obtained in good yields (71−87%, entries 6−9). It is noted that the highest enantioselectivity (entry 6, 99% ee) was achieved when *p*-methylaniline (**3g**) was used. Good enantioselectivities were observed in the presence of *o*- and *m*-trifluoro methylanilines (entries 8 and 9, 82 and 75% ee, respectively). On the basis of these results, we observed that the presence of substituents on the aniline improves stereoselectivity with a little effect on reactivity. α,β-unsaturated carbonyl compounds as 3-penten-2-one leads to secondary amine **4k** alone the one reduction of the double bond C−C, giving a slight enantiomeric excess of 10% (entry 10). It is noteworthy that substituted or sterically hindered aliphatic carbonyl compounds all reacted well to give chiral

**Table 2.** Asymmetric Reductive Amination of Alkyl Ketones[a]




| entry | ketone | amine | product | yield[b] (%) | ee[c] (%) (config) |
|---|---|---|---|---|---|
| | | R$^3$ = | | | |
| 1 |  | **3b** *p*-Me | **4b**  | 84 | 73 (−)[g] |
| 2 | | **3c** *m*-CF$_3$ | **4c** | 51 | 95 (−)[g] |
| 3 |  | **3d** H | **4d**  | 68 | 49 (+)[d,g] |
| 4 | | **3e** *p*-Me | **4e** | 51 | 95 (−)[e,g] |
| 5 |  | **3f** H | **4f**  | 77 | --[f] |
| 6 |  | **3g** *p*-Me | **4g**  | 77 | 99 (−)[e,g] |
| 7 | | **3h** *p*-Et | **4h** | 87 | 92 (−)[g] |
| 8 | | **3i** *o*-CF$_3$ | **4i** | 76 | 82 (+)[e,g] |
| 9 | | **3j** *m*-CF$_3$ | **4j** | 71 | 75 (S)[h] |
| 10 |  | **3k** H | **4k**  | 78 | 10 (−)[d,e,g] |
| 11 |  | **3l** H | **4l**  | 83 | 51 (−)[e,g] |
| 12 | | **3m** *p*-Me | **4m** | 73 | 90 (−)[e,g] |
| 13 |  | **3n** *p*-Et | **4n**  | 80 | 83 (−)[e,g] |
| 14 | | **3o** *o*-CF$_3$ | **4o** | 71 | 82 (−)[e,g] |
| 15 |  | **3p** *m*-CF$_3$ | **4p**  | 74 | 96 (−)[g] |
| 16 |  | **3q** H | **4q**  | 80 | 53(de)(−)[d,g,i] 66(de) |
| 17 |  | **3r** H | **4r**  | 85 | 20 (−)[e,g] |
| 18 | | **3s** *o*-CF$_3$ | **4s** | 83 | 2 (−)[e,g] |

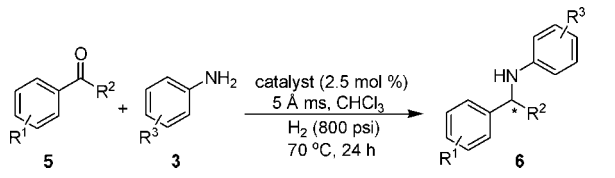
[a] Reactions were carried out with 2.5 mol % of catalyst **1b**, 1.0 mmol of ketone, 1.5 mmol of aniline derivative, 150 mg of 5 Å ms, 10 mL $CHCl_3$, and $H_2$ (800 psi) at 70 °C for 24 h. [b] Isolated yield. [c] The ee values were determined by HPLC. [d] The de and ee values were determined by chiral GC−MS (EI). [e] Realized with catalyst **1c**. [f] Realized with catalyst **1a**. [g] Absolute configurations were not determined. [h] Absolute configuration was determined by derivatizing to 2-butylamine hydrochloride and comparing with the assigned optical rotation reported in the literature. [i] These values correspond to two pairs of diastereomers.

amines (**4l**−**4p**) with moderate to high ee values of 51−96% and yields of 71−83% (entries 11−15). When commercially available, 2-*sec*-butylcyclohexanone (mixture of diastereomers) is used, and chiral amine **4q** was obtained with three chiral centers (entry 16). One would expect a mixture of four

pairs of diastereomers, but interestingly, the mixture has only two pairs of diastereomers with 53 and 66% of diastereomeric excess respectively, which shows also the diastereoselectivity of the reaction using **1b** complex (see Supporting Information). 2,3-Butanedione underwent chemoselective reductive amination with **4r** and **4s** to yield monoaminated products, which were isolated in good yields (entries 17−18, 83−85%) and low enantiomeric excess (20−2% ee).

In all entries, when the crude reaction products were analyzed by GC−MS (EI), we observed that the catalytic palladium system does not promote the reduction of ketone to the corresponding secondary alcohol.

**Table 3.** Asymmetric Reductive Amination of Aryl Ketones[a]




| entry | cat. | $R^1$ | $R^2$ | | $R^3$ | yield[b] (%) | ee[c] (%) (config) |
|---|---|---|---|---|---|---|---|
| 1 | **1b** | H | Me | **5a** | H | 64 | 43 (*R*)[d] |
| 2 | **1c** | *p*-Me | Me | **5b** | *p*-Me | 67 | 38 (+)[e] |
| 3 | **1d** | H | Me | **5c** | *p*-OMe | 65 | 35 (*R*)[d] |
| 4 | **1b** | *p*-Me | Me | **5d** | *p*-OMe | 53 | 38 (+)[e] |
| 5 | **1d** | H | Et | **5e** | *p*-OMe | 57 | 34 (+)[e] |

[a] Reactions were carried out with 2.5 mol % of catalyst, 1.0 mmol of ketone, 1.5 mmol of aniline derivative, 150 mg of 5 Å ms, 10 mL of $CHCl_3$, and $H_2$ (800 psi) at 70 °C for 24 h. [b] Isolated yield. [c] The ee values were determined by HPLC. [d] Absolute configurations were determined by comparison of optical rotation reported in the literature. [e] Absolute configurations were not determined.

A series of aryl ketones (**5a**−**e**) were subjected to the asymmetric reductive amination with substituted anilines (Table 3). The reaction occurs generally with moderate yields (entries 1−5, 53−67%) and low enantiomeric excess (34−43%). The simplest aryl ketone **5a** was reductively aminated with 43% ee (entry 1). When the alkyl group of aryl ketone was changed from Me to Et, the ee dropped from 35 to 34% respectively (entries 3 and 5).

It is interesting to note that there are some examples in the asymmetric reductive amination of ketones where aryl ketones are aminated in high ee and aliphatic or cycloaliphatic ketones are aminated in lower ee, which is opposite to what we observed here.[15]

In summary, chiral (diphosphine) palladium(II) dibromide catalysts promote in one-pot the asymmetric reductive amination of aliphatic, cycloaliphatic ketones in good yields with moderate to high enantiomeric excess. It is evident that these palladium systems are effective and induce enantioselectivity on reduction of the iminic intermediate (formed in situ). This stage is probably the limiting step in the transformation.

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**Supporting Information Available:** Experimental procedures, spectral data for all products, chiral GC-MS (EI) or HPLC data, and X-ray structures for **1b** and **1e** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) See references 7, 8, and 10a.