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A Versatile Synthesis of Substituted Benzimidazolium Salts by an Amination/Ring Closure Sequence

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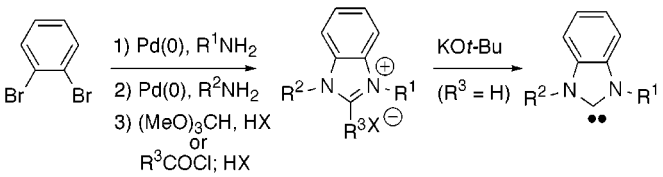
ABSTRACT



A new method to produce benzimidazolium salts based on a successive Buchwald–Hartwig amination and ring closure is reported. A variety of different benzimidazolium salts can be prepared using this procedure. Amines that bear an α-chiral group undergo the reaction to furnish chiral benzimidazolium salts. The salts that lack a C2 substituent on the heterocycle are readily deprotonated to give nucleophilic carbenes.

There remain fundamental questions about the factors which most affect the reactivity of *N*-heterocyclic carbenes.[1] Nonetheless, applications of these carbenes as ligands in the general area of metal-based catalysis have become well-known.[2] The basis for the enhanced reactivity of metal catalysts using the *N*-heterocyclic carbene is based on the ligand's σ donicity.[3] Our interest in benzimidazole carbenes and in *N*-heterocyclic carbenes in general stems from questions concerning the nucleophilicity of the carbenes themselves. To begin to address nucleophilicity, a method was needed that could produce a range of carbenes in order to probe electronic and structural issues. Knowledge of nucleophilicity is expected to aid further organometallic catalyst design and to facilitate applications of the carbenes as nucleophilic catalysts.

N-Heterocyclic carbenes can be generated by deprotonation of the corresponding azolium salts.[4] Our experience with benzimidazole carbenes led us to adopt this direct approach

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(2) (a) Herrmann, W. A.; Kocher, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2162−2187. (b) Bourissou, D.; Guerret, O.; Gabbaie, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39−91. (c) Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2490−2493. (d) Weskamp, T.; Kohl, F. J.; Hieringer, W.; Gleich, D.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 2416−2419. (e) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247−2250. (f) Jafarpour, L.; Nolan, S. P. *Organometallics* **2000**, *19*, 2055−2057. (g) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204−2207. (h) Ackermann, L.; Fürstner, A.; Weskamp, T.; Kohl, F. J.; Herrmann, W. A. *Tetrahedron Lett.* **1999**, *40*, 4787−4790. (i) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402−3415. (j) Lee, H. M.; Smith, D. C., Jr.; He, Z.; Stevens, E. D.; Yi, C. S.; Nolan, S. P. *Organometallics* **2001**, *20*, 794−797. (k) Fürstner, A.; Leitner, A. *Synlett* **2001**, 290−292. (l) Huang, J.; Grasa, G.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307−1309. (m) Fürstner, A.; Krause, H. *Adv. Synth. Catal.* **2001**, *343*, 343−350. (n) Enders, D.; Gielen, H. *J. Organomet. Chem.* **2001**, *617−618*, 70−80. (o) Enders, D.; Gielen, H.; Raabe, G.; Runsink, J.; Teles, J. H. *Chem. Ber.* **1996**, *129*, 1483−1488. (p) Lee, H. M.; Jiang, T.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2001**, *20*, 1255−1258.

(3) Enthalpy of binding to metals and chalcogens has been measured by calorimetry: (a) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 2674−2678. (b) Huang, J.; Schanz, H.-J.; Stevens, E. D.; Nolan, S. P.; Capps, K. B.; Bauer, A.; Hoff, C. D. *Inorg. Chem.* **2000**, *39*, 1042−1045. (c) Huang, J.; Jafarpour, L.; Hillier, A. C.; Stevens, E. D.; Nolan, S. P. *Organometallics* **2001**, *20*, 2878−2882.

(4) An alternative approach involves desulfurization of the thiourea: (a) Kuhn, N.; Kratz, T. *Synthesis* **1993**, 561−562. (b) Denk, M. K.; Thadani, A.; Hatano, K.; Lough, A. J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2607−2609. (c) Hahn, F. E.; Wittenbecher, L.; Van, D. L.; Fröhlich, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 541−544. (d) Kuhn, N.; Niquet, E.; Steimann, M.; Walker, I. *Z. Naturforsch. B* **1999**, *54*, 1181−1187. (e) Karkhanis, D. W.; Field, L. *Phos., Sulfur* **1985**, *22*, 49−57. (f) Arduengo, A. J.; Goerlich, J. R.; Krafczyk, R.; Marshall, W. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1963−1965. (g) Faust, R.; Göbelt, B. *Chem. Commun.* **2000**, 919−920.

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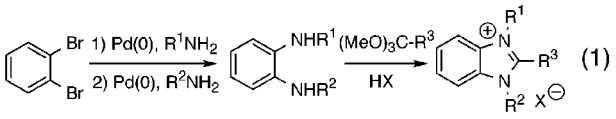
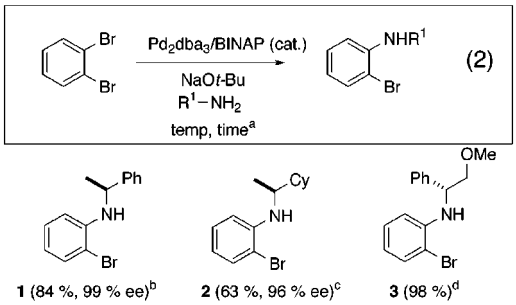
using benzimidazolium salts as the carbene precursors. However, the literature methods for the synthesis of benzimidazolium salts have generally focused on *N*-alkylation reactions which are limited to reactive halides and are inappropriate for introduction of chiral substituents. In this report, we provide a new method for the synthesis of benzimidazolium salts containing a wide variety of substitution patterns (eq 1). The effectiveness of the method allows for the generation of benzimidazolium salts which bear C2 substituents as well.



Our approach to carbene synthesis requires the availability of the azolium precursors. Chiral *N*-substituted imidazolium salts have been synthesized by a three-component condensation, a method that is suitable for the incorporation of α-chiral primary amines into the imidazolium ring.[5] The Grubbs group has prepared dihydroimidazole carbenes in situ from the dihydroimidazolium salts[6] used in the preparation of the highly active ruthenium carbene metathesis catalyst.[7] Importantly, the Grubbs paper[7a] also reported ruthenium complexes made from the corresponding chiral dihydroimidazolium salt produced through chiral diamine amination with bromoarenes.[6b] Despite these advances, to the best of our knowledge, there is no available method for introducing chiral, nonracemic substituents on the nitrogen atoms of the benzimidazolium nucleus.[8] Recent developments in the Buchwald−Hartwig reaction have facilitated the mild introduction of chiral amines onto aromatic rings.[9] The palladium-catalyzed amination is also suitable for preparing polyanilines including 1,2-benzenediamines, indicating a tolerance for electron-rich aromatic halides.[10]

Our synthetic approach toward *N*-substituted benzimidazolium ions relies on Pd-catalyzed amination of dibromobenzene. This process has proven versatile for simultaneous and stepwise introduction of amines resulting in symmetrical or unsymmetrical 1,2-benzenediamines, respectively. To illustrate the flexibility of our approach, monobromoanilines were chosen as starting materials, available through a controlled monoamination reaction (Scheme 1). Each reaction

Scheme 1. Preparation of Chiral Monobromoanilines



a) 1.0−2.0 mol % Pd_2dba_3, 2.0−6.0 mol % BINAP, 1.2−1.5 eq. NaO*t*-Bu, 1.0−1.2 eq. amine; *Specific conditions*: b) 95 °C, 48 h; c) 110 °C, 14 h; d) 80 °C, 48 h.

was optimized with respect to temperature and time. In the case of **1** and **2**, enantiomeric excess determinations indicated that no racemization was occurring competitively with C−N bond formation. The major byproducts in most cases were the corresponding aniline (via reduction) and the corresponding symmetrical dianiline. The competing reduction of sterically hindered bromoarenes is thought to occur as a result of intermediate palladium hydrides. It has been shown that bulky phosphines and chelating diphosphines such as BINAP are effective in suppressing the β-elimination pathway leading to Pd−H, the pathway that also leads to racemization of α-chiral primary amines.[11] The diphosphine BINAP proved to be the most versatile ligand in the couplings of Scheme 1.

Benzimidazolium salts were constructed by a second amination and a subsequent ring closure step (Table 1). In the amination of **1** with α-methylbenzylamine, optimized reaction conditions have already been reported.[10c] Careful attention to reaction conditions proved critical in order to suppress epimerization (entries 1 and 2) which was assayed by ^{1}H NMR and hplc. The cyclization step can be conducted with one equivalent of the appropriate strong acid (HCl in entries 1,3−5; $HClO_4$ in entry 2). Typically, the salt precipitated from the cooled solution. Counterion exchange proved beneficial for the isolation of **10**, the BPh_4 salt obtained by treating the crude chloride salt with $NaBPh_4$ in CH_3CN. All of the salts in Table 1 are new compounds and were characterized by spectral and elemental analyses.[12]

The present work was prompted by a need to generate benzimidazole carbenes from the prepared benzimidazolium

(5) (a) Herrmann, W. A.; Goossen, L. J.; Köcher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2805−2807. (b) Herrmann, W. A.; Goossen, L. J.; Artus, G. R. J.; Köcher, C. *Organometallics*, **1997**, *16*, 2472−2477. (c) Arduengo, A. J. U.S. Patent 5,077,414, 1991. (d) Gridnev, A. A.; Mihaltseva, I. M. *Synth. Commun.* **1994**, *24*, 1547−1555. (e) Arduengo, A. J.; Krafczyk, R.; Schmutzler, R. *Tetrahedron*, **1999**, *55*, 14523−14534.

(6) (a) Saba, S.; Brescia, A.; Kaloustian, M. K. *Tetrahedron Lett.* **1991**, *32*, 5031−5034. (b) Cabanal-Duvillard, I.; Mangeney, P. *Tetrahedron Lett.* **1999**, *40*, 3877−3880.

(7) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956. (b) Sanford, M. S.; Ulman, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 749−750.

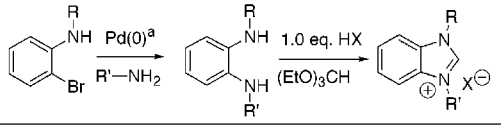
(8) Direct alkylation of benzimidazole is possible but produces a mixture of enantiomers and diastereomers. Preparation of *N*-*sec*-phenethylbenzimidazole: Simonov, A. M.; Pozharskii, A. F. *Zh. Obshch. Khim.* **1964**, *34*, 1572−1574.

(9) (a) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215−7216. (b) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217−7218. Reviews: (c) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805−818. (d) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2047. (e) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146.

(10) (a) Witulski, B.; Senft, S.; Thum, A. *Synlett* **1998**, 504−506. (b) Beletskaya, I. P.; Bessmertnykh, A. G.; Guilard, R. *Tetrahedron Lett.* **1999**, *40*, 6393−6397. (c) Rivas, F. M.; Riaz, U.; Diver, S. T. *Tetrahedron: Asymmetry* **2000**, *11*, 1703−1707.

(11) Mechanistic work on the β-elimination pathway: (a) Hartwig, J. F.; Richards, S.; Baranano, D.; Paul, F. *J. Am. Chem. Soc.* **1996**, *118*, 3626−3633. (b) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451−8458.

Table 1. Benzimidazolium Salts by Amination/Ring Closure

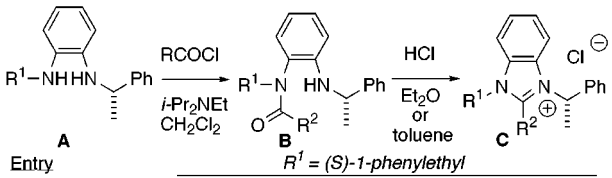


entry			
		R = (S)-1-phenylethyl	
1	**1** (99 % ee)	**4,** R' = *(S)*-1-phenylethyl, 70 % yield (99 % ee)[b,c]	**5,** R' = *(S)*-1-phenylethyl, X=Cl, 99 % yield
2	**1** (99 % ee)	**4,** R' = *(S)*-1-phenylethyl	**6,** R' = *(S)*-1-phenylethyl, X=ClO_4,86 % yield
3	1 (99 % ee)	**7,** R' = Ph, 92 % yield (99 % ee)	**8,** R' = Ph, X=Cl, 97 % yield
		R = (S)-1-cyclohexylethyl	
4	**2** (96 % ee)	**9,** R'=Ph, 96 % yield (98 % ee)	**10,** R'=Ph, X=BPh_4, 83 % yield
		R = (S)-1-phenyl (2-methoxy)ethyl	
5	**3**[d]	**11,** R'=Ph, 78 % yield[d]	**12,** R'=Ph, X=Cl, 91 % yield

(a) 3.4-4.0 mol % Pd_2dba_3, 6.8-8.0 mol % BINAP, 1.3-2.0 eq. NaO*t*-Bu, toluene, 80-135 °C; see Experimental for the specific conditions used in each entry. (b) Isolated yields. (c) >95 % de for **4**. (d) **3:** $[\alpha]^{25}_D$= +119 (c=4.2, CH_2Cl_2); **11:** $[\alpha]^{25}_D$= +168 (c=2.6, CH_2Cl_2)

salts of Table 1; however, the scope of the bisamination/ring closure encompasses C-2 substituted benzimidazolium salts.[13] By a slight modification, a variety of R groups can be introduced into the C-2 position by acylation of diamine **A** with an acid chloride (Table 2). In this case, ring closure

Table 2. C-2-Substituted Benzimidazolium Salts

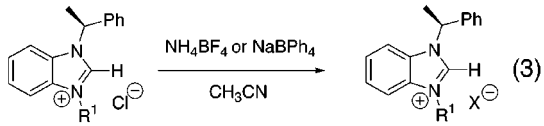


Entry		
	R^1 = (S)-1-phenylethyl	
1	**13**, R^2 = Me, 91 %	**19**, R^2 = Me, 90 %
2	**14**, R^2 = Et, 87 %	**20**, R^2 = Et, 87 %
3	**15**, R^2 = Ph, 75%	**21**, R^2 = Ph, 84 %
	R^1 = Butyl	
4	**16**, R^2 = CH_3, 97 %	**22**, R^2 = CH_3, 98 %
5	**17**, R^2 = Ph, 98 %	**23**, R^2 = Ph, 87 %
	R^1 = Phenyl	
6	**18**, R^2 = Ph, 87 %	**24**, R^2 = Ph, 67 %

is accomplished by reaction of **B** with 1 equiv of the desired acid to provide the salts **19**−**24**.

Solubility and handling of the prepared benzimidazolium salts in organic solvents can be improved by counterion exchange.[14] Three examples of the ion exchange are provided

Scheme 2. Soluble Benzimidazolium Salts via Anion Exchange



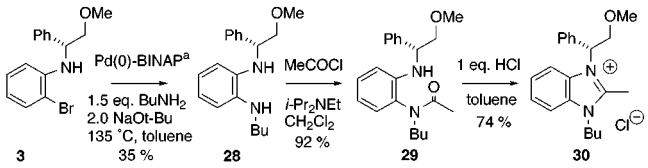
5 R^1 = (S)-1-phenylethyl
5 R^1 = (S)-1-phenylethyl
8 R^1 = Ph

25 X=BF_4, 97 %
26 X=BPh_4, 99 %
27 X=BPh_4, 97 %

in Scheme 2, and one example appears in entry 4 of Table 1. For example, the ion pair **26** proved to be highly soluble in common organic solvents (CH_2Cl_2, $CHCl_3$, THF, CH_3CN, EtOAc, acetone) and was more easily handled on the benchtop than the hygroscopic chloride salts which became gels on exposure to the atmosphere.[15]

Other chiral substituents in addition to α-methylbenzylamine could be used in the reaction sequence. For instance, phenylglycinol-derived monobromide **3** was coupled to $BuNH_2$ and acetylated to give a mixture of amide rotamers that were cyclized with 1 equiv of HCl in toluene to give salt **30** (Scheme 3). The main side reaction in the coupling step was reduction of bromide **3**.

Scheme 3. Introduction of Additional Chiral Substitution



conditions: (a) 4 mol % Pd_2dba_3, 8 mol % (±) BINAP

Benzimidazolium salts are precursors to nucleophilic carbenes by deprotonation. The downfield carbene carbon chemical shift is diagnostic.[4b,c,16] For dihydroimidazole carbenes, Wanzlick carbenes **I** (Scheme 4) and imidazole carbenes **II**, the chemical shift is quite different, ca. 238 and 215 ppm, respectively.[4b,16c] Benzimidazole carbenes display a carbene chemical shift intermediate between the aforementioned carbenes, although it has been suggested that benzimidazole carbenes are more like saturated carbenes.[16a] Deprotonation of salt **26** (KO*t*-Bu, THF) produces carbene **31** (eq 4), which displays a ^{13}C chemical shift of 224.0 ppm

(12) For the benzimidazolium salts in Table 1, the chemical shift of the C2 proton was diagnostic: ca. 12 ppm for the chloride salts. **5** displays a chemical shift of 12.52 ppm ($CDCl_3$) for the C2 proton; the perchlorate salt, 9.93 ppm; the Ph_4B salt, 7.03 ppm.

(13) Phase transfer-catalyzed allylation of the benzophenone imine of glycine *tert*-butyl ester using catalyst **19** gave a 92% yield of monoallylated product of 31% ee. Further studies are in progress.

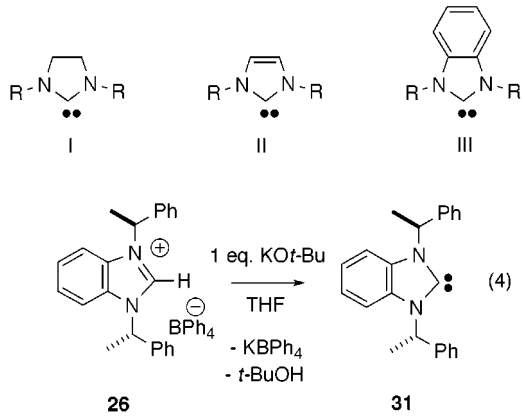
(14) Use of $AgPF_6$: Shi, Z.; Thummel, R. P. *Tetrahedron Lett.* **1994**, *35*, 33−36.

(15) Compound **5** is not soluble in THF or ethyl acetate; **5** is soluble in CH_3CN, $CHCl_3$, and CH_2Cl_2.

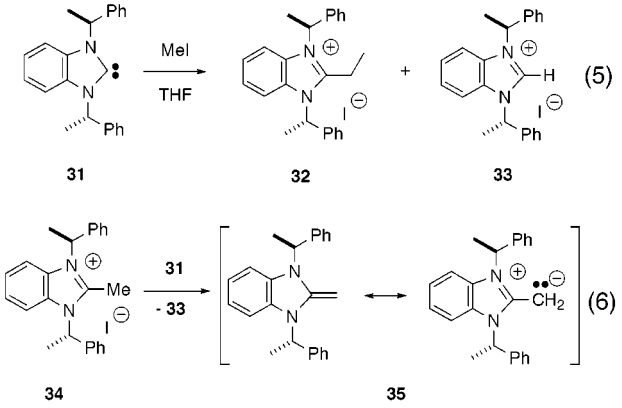
(16) (a) Hahn, F. E.; Wittenbecher, L.; Boese, R.; Bläser, D. *Chem. Eur. J.* **1999**, *5*, 1931−1935. (b) Liu, Y.; Lindner, P. E.; Lemal, D. M. *J. Am. Chem. Soc.* **1999**, *121*, 10626−10627. (c) Arduengo, A. J.; Dias, R. H. V.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1992**, *114*, 5530−5534.

(17) The nucleophilicity of **35** is akin to an enamine; however, the aromatic resonance contributor probably enhances the nucleophilicity of the enamine terminal carbon atom. (a) For relevant study reporting the methylation of an enamine similar to **35**, see: Bourson, J. *Bull. Soc. Chim. Fr.* **1971**, 3541−3547. (b) Study of an imidazole-2-methylidene: Arduengo, A. J.; Davidson, F.; Dias, H. V. R.; Goerlich, J. R.; Khasnis, D.; Marshall, W. J.; Prakasha, T. K. *J. Am. Chem. Soc.* **1997**, *119*, 12742−12749.

Scheme 4. Carbene Families



Scheme 5. Alkylation of Carbene **31** with MeI



in d_8-THF. This value is consonant with related nucleophilic carbenes. Like Wanzlick carbenes, the benzimidazole carbenes of type **III** have a widened N−C−N bond angle and show a tendency to dimerize, chemical behavior that has been independently studied by Hahn[4c] and Liu.[16b] Beyond dimerization, it has not been shown how the structural differences of the benzimidazole carbene will influence reactivity.[16]

Initial studies of the nucleophilicity of carbene **31** led to a surprising result. Generation of the benzimidazole carbene using 1.0 equiv of KO*t*-Bu in THF and filtration of the salts produced the free carbene. Alkylation with an excess of iodomethane gave the C2-*ethylated* benzimidazolium salt **32** along with ca. 0.5 equiv of C-2 protio salt **33**, recovered as its iodide (Scheme 5). A likely interpretation of this result is that the intermediate salt **34** was deprotonated by unalkylated carbene to give betaine **35** which underwent alkylation by the excess MeI.[17] Further alkylation studies are in progress.

In summary, a versatile method for the synthesis of a variety of benzimidazolium salts has been detailed. The method is suitable for the preparation of C2-substituted salts and benzimidazolium salts that bear chiral substituents on either one or both of the nitrogen atoms. The salts could be deprotonated to generate the benzimidazole carbenes. A more detailed investigation of the nucleophilicities of benzimidazole carbenes derived from the new C2-unsubstituted benzimidazolium salts will be reported in due course.

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Supporting Information Available: Experimental procedures for the synthesis of salts and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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