Communications

Homogeneously Catalyzed Synthesis of β-Amino Alcohols and Vicinal Diamines from Ethylene Glycol and 1,2-Propanediol

Summary: Disubstituted β-amino alcohols and tetrasubstituted vicinal alkanediamines have been synthesized in high yield and at mild temperatures by the selective amination of ethylene glycol and 1,2-propanediol catalyzed by ruthenium or iridium complexes.

Sir: Alternative syntheses of β-amino alcohols and vicinal diamines from readily available starting materials have recently received some attention.[1,2] The usual methods of synthesis from epoxides and vicinal dihalides are not always applicable, especially for molecules of biological interest. We now report the facile, selective synthesis of *either* β-amino alcohols (i.e., monoamination, eq 1) *or* vicinal diamines (i.e., diamination, eq 2) from alkanediols and secondary amines with the selectivity controlled by the proper choice of soluble metal catalyst. Similar cat-

$$HOCH_2CH_2OH + HNR_2 \rightarrow HOCH_2CH_2NR_2 + H_2O \quad (1)$$

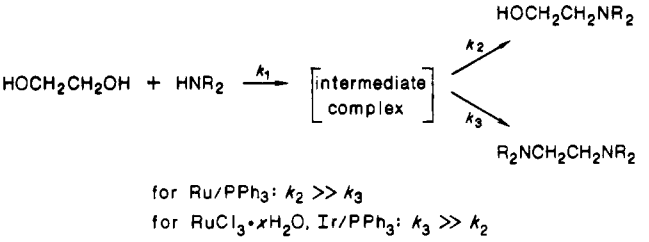
$$HOCH_2CH_2OH + 2HNR_2 \rightarrow R_2NCH_2CH_2NR_2 + 2H_2O \quad (2)$$

alysts have been utilized to effect aminations of monoalkanols[3-6] as well as N-heterocyclizations of 1,4-, 1,5-, and 1,6-diols.[7,8] However, to our knowledge, this is the first example of selectivity control in the amination of vicinal diols with homogeneous catalysts.

In a typical reaction, a 22-mL Parr bomb reactor was charged in an inert atmosphere (N_2) glovebox with catalyst (ca. 1.2×10^{-4} mol contained metal), amine (ca. 1.2×10^{-2} mol), and diol (ca. 5 mL). After the addition of an internal standard (usually *N*-methylpyrrolidone), the bomb was placed in a previously heated oil bath and the contents agitated by means of a magnetic stirring bar under autogenous pressure. After a suitable reaction time, the bomb was cooled, vented, and opened. The reaction mixture was then centrifuged and the liquid analyzed by GLC. With the less volatile amines, the reactions could be run in a flask fitted with a reflux condenser. When this was possible, such reactions showed little difference from those run in the bomb reactor.

The reaction of ethylene glycol (excess) with secondary amines proceeds smoothly at 100–120 °C in the presence of $RuCl_2(PPh_3)_3$ to give high yields of tertiary amino alcohols (Table I). In order to quantify the selectivities of

Scheme I



our reactions, we have chosen to define a selectivity ratio, *r* (eq 3). This selectivity ratio is tabulated in Table I and

$$r = \frac{\text{selectivity to diamine}}{\text{selectivity to amino alcohol(s)} + \text{selectivity to diamine}} \quad (3)$$

shows that $RuCl_2(PPh_3)_3$ is quite selective for the monoamination of ethylene glycol (i.e., $r \rightarrow 0$). As may be expected, $RuHCl(PPh_3)_3$ and $RuCl_3 \cdot xH_2O/3PPh_3$ give selectivities and activities virtually identical with those of $RuCl_2(PPh_3)_3$.

In contrast, $RuCl_3 \cdot xH_2O$ *without* added PPh_3 gives high selectivity to tertiary ethylenediamines (Table II, $r \rightarrow 1$). Selectivity varies smoothly toward diamination as the ratio of PPh_3 to Ru is decreased. This effect is shown in Table III, with large excesses of PPh_3 giving almost complete selectivity to monoamination. In addition, $IrCl_3 \cdot xH_2O$ with added PPh_3 (3 mol of PPh_3/mol Ir) is also an efficient catalyst for the reaction described by eq 2. Without added triphenylphosphine, $IrCl_3 \cdot xH_2O$ shows almost no catalytic activity for this reaction.

The activity seen for $RuCl_3 \cdot xH_2O$ in the absence of phosphine additive is particularly noteworthy and surprising. Watanabe reports no activity for this species with aromatic amines as substrates,[5,8] while Porzi indicates that $RuCl_3 \cdot xH_2O$ together with smaller amounts of PPh_3 (PPh_3/Ru = 2) gave poor and irreproducible results in closely related alkyl group redistribution reactions of alkyl amines.[9] We have found that high, reproducible conversions and selectivities are attainable with $RuCl_3 \cdot xH_2O$, but an induction period of a variable length of from 1 to 5 h is seen. The varying length for the induction period is probably related to the ill-defined nature of $RuCl_3 \cdot xH_2O$[10] and is currently the subject of a more extensive investigation in our laboratories.

We have included two entries for $RuCl_3 \cdot xH_2O$ in Table III. It should be stressed that these apparently inconsistent conversions are due only to the variable induction period and do not reflect differences in actual catalyst activity. If the induction period is recognized, however, consistently high conversions can be obtained. It should be noted that selectivity for a given catalyst is relatively invariant with respect to amine conversion. The selectivity to diamination falls off rather quickly as the amount of PPh_3 is increased, with monoamination strongly favored

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Table I. Monoamination of Ethylene Glycol[a] with Secondary Amines

amine	catal[b]	time, h	conv, %	selectivity, %[c] $R_2NCH_2CH_2OH$	selectivity, %[c] $R_2NCH_2CH_2NR_2$	r[d]
morpholine	A	2	100	83	9	0.10
morpholine	B	5.5[e]	94	90	2	0.02
morpholine	C	2	95	88	2	0.02
pyrrolidine	A	6	100	79	obsd	
Me_2NH	A	3	100	81	4	0.05
Et_2NH	A	2	98	91	1	0.01

[a] As solvent (5 mL), t = 120 °C. [b] Key: A = $RuCl_2(PPh_3)_3$, B = $RuHCl(PPh_3)_3$, C = $RuCl_3 \cdot xH_2O/3PPh_3$, all ca. 2×10^{-2} M (1 mol % based on amine). [c] By GLC. [d] See text for definition. [e] t = 100 °C.

Table II. Diamination of Ethylene Glycol with Secondary Amines[a]

amine	catal[b]	conv, %	selectivity, % $R_2NCH_2CH_2OH$	selectivity, % $R_2NCH_2CH_2NR_2$	r[c]
morpholine	D	100	16	80	0.83
morpholine	E	79	10	80	0.89
Me_2NH	D	100	11	85	0.88
Me_2NH	E	76	9	63	0.88
Et_2NH	D	42	15	83	0.85

[a] Reaction conditions as in Table I, 2–2.5 h reaction time. [b] Key: D = $RuCl_3 \cdot xH_2O$, E = $IrCl_3 \cdot xH_2O/3PPh_3$, concentration ca. 2×10^{-2} M. [c] See text for definition.

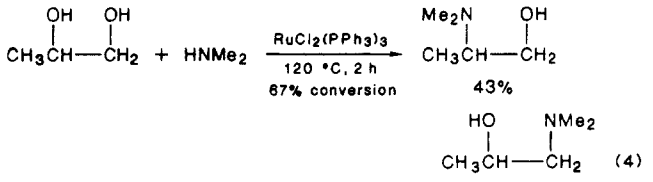
Table III. Effect of PPh_3–Ru Ratio on Selectivity of Ethylene Glycol Reactions with Morpholine[a]

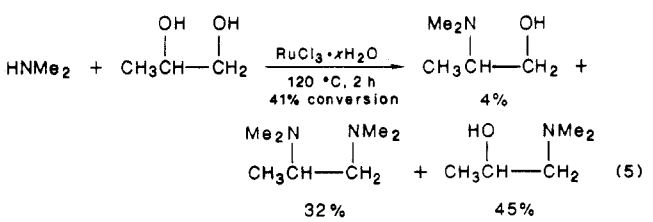
PPh_3–Ru[b] ratio	conv, %	selectivity, % $R_2NCH_2CH_2OH$	selectivity, % $R_2NCH_2CH_2NR_3$	r[c]
0	60	7	75	0.91
0	100	17	80	0.83
0.5	53	43	48	0.53
1	79	70	20	0.22
3	95	88	4	0.04
11	100	94	<0.01	<0.01

[a] Conditions as in Table I, 2–2.5 h reaction time. [b] Concentration of $RuCl_3 \cdot xH_2O$ held constant at ca. 2×10^{-2} M. [c] See text for definition.

when as little as 1 mol of PPh_3/mol of Ru is present.

In the case of 1,2-propanediol, the amination is again efficiently catalyzed, but with lesser substitution selectivity. With $RuCl_2(PPh_3)_3$, monoamination with $HNMe_2$ smoothly proceeds to the two isomeric products (r = 0.06) (eq 4). With $RuCl_3 \cdot xH_2O$, however, the major products are the diamine and the 1,2-amino alcohol (eq 5). While there





is clearly an increase in the yield of diamine by the use of the phosphine-free catalyst (r = 0.39), the overall selectivity control that can be achieved is much less than when ethylene glycol is used as the substrate.

The remarkable selectivity control demonstrated by these catalyst systems has led us to undertake some preliminary mechanistic studies. We have established that the addition of *N*-(hydroxyethyl)morpholine (HEM) to a reaction of morpholine and ethylene glycol catalyzed by $RuCl_3 \cdot xH_2O$ does not lead to an increase in the rate of formation of the diamine nor is the added HEM consumed. This indicates that "free" (i.e., nonmetal coordinated) HEM is *not* an intermediate in the diamination reaction, suggesting that diamination occurs in a one-step process. This is consistent with mono- and diamination arising from a common intermediate (see Scheme I).

We suspect the intermediate is a *N*,*N*-dialkylethanolamine complex, which in the absence of PPh_3 is sufficiently long-lived to activate the remaining hydroxy group toward substitution. In the presence of PPh_3, the ethanolamine complex dissociates to give free monoaminated product. With $IrCl_3 \cdot xH_2O/3PPh_3$, diamination presumably occurs because third row metal complexes are generally less labile than those of the second row,[11] sufficiently stabilizing the ethanolamine complex against dissociation to allow diamination to occur, even in the presence of PPh_3.[12]

For the amination of diols, the selectivity achievable with these homogeneous catalysts contrasts sharply with that attainable with traditional heterogeneous alcohol amination catalysts. We are exploring these systems further in order to increase the scope and utility of selective alkanediol amination.

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Registry No. $RuCl_2(PPh_3)_3$, 15529-49-4; $HO(CH_2)_2OH$, 107-21-1; Me_2NH, 124-40-3; Et_2NH, 109-89-7; $Me_2N(CH_2)_2OH$, 108-01-0; $Et_2N(CH_2)_2OH$, 100-37-8; $RuHCl(PPh_3)_3$, 55102-19-7; $RuCl_3$, 10049-08-8; PPh_3, 603-35-0; $IrCl_3$, 10025-83-9; $Me_2N(CH_2)_2NMe_2$, 110-18-9; $Et_2N(CH_2)_2NEt_2$, 150-77-6; morpholine, 110-91-8; pyrrolidine, 123-75-1; *N*-morpholineethanol, 622-40-2; 4,4′-(1,2-ethanediyl)bismorpholine, 1723-94-0; 1-pyrrolidineethanol, 2955-88-6.

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(12) The mechanism by which alcohol amination itself occurs has not been rigorously examined, although possible mechanisms have been suggested. See e.g., ref 4 and 8.

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