Nucleophile Study:

Drag out that lovely, faded, rusty, abused pka table and start looking in the base columns. Notice that many of the compounds have negative charges and ALL of them are nucleophiles because they have a source of electrons.

Consider what makes a nucleophilic atom a good "attacker" – nucleophilicity is measured as a rate – how fast can the nucleophile attack a simple alpha carbon, like CH$_3$Br for instance. Nucleophilicity trends tend to go in the opposite direction from electronegativity trends (although this is mainly due to protic solvent effects in the halogen trends). However, this means that good nucleophilic atoms could be good bases (especially as you move left across the second row in the periodic table at the elements that are anions (N$^-$, O$^-$, C$^-$). Basicity trends match nucleophilicity trends in this direction, and that is the reason that sometimes SN2 can "go bad" in focus, leading to E2. The nucleophile is usually the most important reagent to analyze when determining focus.

The questions facing you as you evaluate your nucleophiles are:

1) is it a bad base? will the nucleophile attack ONLY the alpha carbon? Nucleophilic sites (remember it is an individual atomic site in the nucleophile that does this job – you have to look very closely at that atom and the electrons around that atom) that are weakly basic, will be more inclined to find a carbon atom than a proton.

Look on the base column, starting with the weakest in the upper left: Halides (I$^-$, Br$^-$, etc.), are great nucleophiles that do NOT take off protons well). They are also smallish, single atoms.

Keep looking...in general, most of the bases up until hydroxide (Use water as your reference point in the acid column, pKa 15.7) are considered weak bases. Get a feeling about how and why they are weak. Neutral N (9.4), −CN (9.1), CH$_3$S$^-$ (10.5), resonance stabilized oxyanions (like CH$_3$COO$^-$ at 4.8) – all of these are negative in character, most of them have full or partial negative charge, but none of them can get a proton and hold it well. This limits their
ability to detect protons, they are less likely to be distracted by protons (Hs on beta Carbons) and, hence QED, they will primarily attack alpha carbons.

2) Is it a good base?: Now look at the others, above that 15.7 pka dividing line. Most of the strong bases contain negatively charged O, N, or C atoms. These things CAN detect protons, they can attack protons, and therefore they are likely to be distracted by, and sometimes completely focused on, beta Hs.

Remember that a nucleophile does not have to be EITHER a good nucleophile OR a good base – sometimes it can be both!

Of course, the larger the base is, the more likely it is to be focused on protons (and kinetically, it may be focused on easier to reach protons more than hidden ones...another topic for Friday) because it cannot reach that tetrahedral alpha carbon. To see this trend consider:

- OH, -OCH3, -OC(CH3)3 (the big strong base) – hydroxide is far more able to act as a nucleophile attacking an alpha carbon than the big strong tertiary-butoxide base. SN is more possible for -OH, assuming the alpha carbon is accessible.

Similarly, look at 26, 36, and 49 Carbons (spC-, sp2C-, sp3C-) all are carbon nucleophiles and strong bases, but the skinniest C is more able to get to an alpha carbon than the others are.

These trends do NOT suggest that substitution is the only path for the skinny, smaller strong bases – they are still very able to do elimination.....that is why some reactions result in mixed products and mixed mechanisms....

3) Is it just plain WEAK – weak at everything? Waiters....all of them. Water and alcohols are in the weak base area of the pKa table. But they are also considered weak nucleophiles – they are neutral and an O atom is not likely to desire a positive charge (in contrast, a N is much more able to carry a + charge and is much more nucleophilic!).
Why pick a weak reagent? To avoid elimination? maybe, but typically these reagents are also protic solvents and their behavior as solvents is mixed into their behavior as nucleophiles.

* Protic solvents can H–bond – this slows down stronger nucleophiles (like F– or Cl–, or oxyanions) by making them less charged and making them drag around solvent molecules. For this reason protic solvents slow down SN2 reactions that are favored with these kinds of nucleophiles, and aprotic solvents speed up bimolecular reactions.

* Protic solvents are very polar and they encourage (speed up) carbocation formation. This means that protic solvents increase the rate of unimolecular mechanisms. Warning: solvents do not force C+ formation – that is still determined by the alpha carbon).

If a weak nucleophile, a protic solvent, is the ONLY nucleophile present: unimolecular madness ensues....

Get familiar with that pka table.....