From: Real World Cases in Green Chemistry (2000),
Michael C. Cann and Marc E. Connelly, American
Chemical Society, 5-12.

The Concept of
Atom Economy[1]

How Many Reactant Atoms Are Incorporated into the Desired Product and How Many Are Wasted?

Overview

Chemical industries that deal with large volumes of chemicals (such as commodity chemical and petrochemical industries) tend to incorporate a high percentage of the atoms in their starting materials into the desired final product (good atom economy), thus minimizing waste byproducts.[2–4] However, chemists who work in the areas of fine chemicals and pharmaceuticals, as well as academic chemists, have traditionally opted for reactions that have high selectivity and high yields.[2–6]

Problem. *With selectivity and yield being the primary concerns in these areas of chemistry, the efficient use of reactants from the standpoint of atom economy is often ignored.[4–8] When these reactants are used inefficiently (few of their atoms are incorporated into the final product) their atoms wind up, in part, as waste byproducts of the reaction.[2,3,5]*

Solution. *The concept of atom economy, a term coined by Barry Trost of Stanford University, considers the amount of starting materials incorporated into the desired final product.[8] The goal of atom economy is to create syntheses in which most (or ideally all) of the atoms of the reactants become incorporated into the desired final product.[3,4] By incorporating a greater amount of the atoms contained in the starting materials (reactants) into the desired product, fewer waste byproducts are created. Thus, by using this concept of atom economy along with the ideas of selectivity and yield, "greener," more efficient syntheses can be developed.[2–5]*

Background

Often, the primary concern of chemists is to produce syntheses that offer good selectivity and high yield of the desired product. Selectivity is concerned with controlling reactions so that the desired product is produced over competing side products.[2] Selectivity can be broken down into different subcategories, namely chemoselectivity, regioselectivity, enantioselectivity, and diastereoselectivity.[9]

Chemoselectivity is the ability to react with one particular functional group over other functional groups found in the reactant(s). Selectively reacting with one functional group can often be a problem when other functional groups compete in the reaction (note the need for a protecting group to prevent the keto functional group from reacting with the Grignard reagent in Scheme 5). Regioselectivity is the ability to control the connectivity between molecules so that one constitutional isomer is favored over another. Enantioselectivity is the ability to predominantly produce one enantiomer over the other. Finally, diastereoselectivity concerns itself with the predominant formation of one diastereomer when two or more diastereomers are possible.

The yield of a reaction, which is perhaps the most common way of expressing the efficacy of a reaction, is a measure of the quantity of product formed versus the quantity of the limiting reagent. The percentage yield is generally calculated according to the following equation (Formula 1) where the theoretical yield is the maximum yield possible based on the quantity of limiting reagent that is used.

Although chemists have developed many reactions of high selectivity and high yield, many of these reactions earn low marks for the incorporation of reactant atoms into the desired product.[4,5,7,8] A significant portion of these atoms of the reactants are found in unwanted waste byproducts, even in reactions that are judged highly efficient based on their high selectivity and high yield.

$$\%\ \text{Yield} = \frac{\text{Actual yield of product}}{\text{Theoretical yield of product}} \times 100$$

FORMULA 1

Green Chemistry: The Concept of Atom Economy

Atom economy proposes that in addition to the selectivity and percent yield of the reaction, one must consider how efficiently atoms of the reactants are used in a chemical synthesis. The concept of atom economy, as developed by Barry Trost, is a consideration of "how much of the reactants end up in the final product."[8] Thus, atom economy takes a look at the atoms that are found in the reactants and then considers how many of them find their way into the desired product and how many of them result in the formation of waste byproducts.

The ideal situation, in terms of atom economy, is to create a synthesis in which all of the atoms in the reactants are incorporated into the final product, because this reaction, in theory, would not produce any waste byproducts. When high atom economy results in significant loss of selectivity and/or lower yield then the goal is to create syntheses that generate the lowest quantity of waste and the most benign waste possible while maintaining high selectivity and high yield.[2,3]

The concept of atom economy has been quantified by Roger A. Sheldon, a professor at Delft University in the Netherlands.[10] Percentage atom utilization is calculated by dividing the molecular weight of the desired product by the molecular weights of all the products generated in a reaction (Formula 2). In many reactions, however, the identities of the waste byproducts are unknown or difficult to determine. Fortunately, conservation of mass allows us to calculate a number similar to the percentage atom utilization called percentage atom economy.[11] We propose to calculate the percentage atom economy by totaling the formula weight of all the atoms in the reactants that are incorporated into the

$$\%\ \text{Atom utilization} = \frac{\text{MW of desired product}}{\text{MW of (desired product + waste byproducts)}} \times 100$$

FORMULA 2

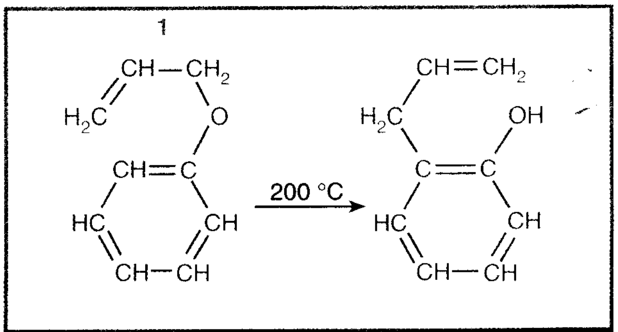
final product (atoms utilized) and divide this number by the total formula weight of all the reactants (Formula 3).

$$\% \text{ Atom economy} = \frac{\text{FW of atoms utilized}}{\text{FW of all the reactants used in the reaction}} \times 100$$

FORMULA 3

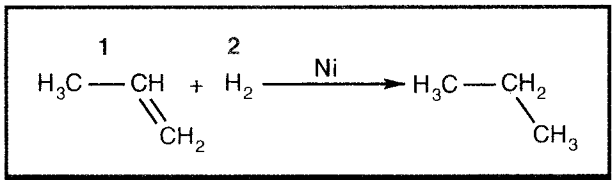
When we look at some common organic reactions (namely, the rearrangement, addition, substitution, and elimination reactions), we will find that some of these reactions are inherently more atom-economical than others. The rearrangement and addition reactions tend to be the most atom-economical, followed by the substitution reaction, and finally, the least atom-economical is the elimination reaction.[7]

A rearrangement reaction is one that changes the connectivity of the starting material, often resulting in a change in the carbon skeleton leading to the formation of the product. Because this reaction pathway simply changes the way the atoms in a molecule are connected (no atoms in the starting materials are lost), it is considered an atom-economical reaction.[7] An example of such a reaction would be the Claisen rearrangement shown in Scheme 1.



SCHEME 1

Note that all the atoms in the reactant (highlighted in green) (1) are found in the final product (also highlighted in green). Thus, to calculate the percentage atom economy (Table 1), one would add up the atomic weights of all the atoms in the reactant that were utilized in the desired product (Table 1, column 2, bottom row), divide this number by the formula weight of the reactant (Table 1, column 1, bottom row), and multiply by 100. Because all of the atoms in the reagent were utilized in the final product, the percentage atom economy (Formula 3) for the Claisen rearrangement is 100% (134.175/134.175 × 100 = 100%).



SCHEME 2

Addition reactions are also atom-economical reactions.[7] In the addition reaction, groups are added to a molecule usually across a double or triple bond. An example of such a reaction is the catalytic hydrogenation of propene (Scheme 2). In this reaction, both of the hydrogen atoms (2) and all of the atoms in the propene molecule (1) are utilized in the final product. Once again, calculating the total atomic weights of the atoms of the reactants that are utilized in the product (Table 2, column 2, bottom row), dividing that number by the total formula weight of all the reactants (Table 2, column 1, bottom row) and multiplying by 100, the percentage atom economy is derived. The percentage atom economy (Formula 3) for this addition reaction is 100% (44.096/44.096 × 100 = 100%). It should also be noted that the nickel used in this reaction is used only in catalytic (not stoichiometric) amounts and can be reused repeatedly.

TABLE 1

	Reagent		**Utilized**		**Unutilized**	
	Formula	**FW***	**Formula**	**FW***	**Formula**	**FW***
1	$C_9H_{10}O$	134.175	$C_9H_{10}O$	134.175	—	—
Total						
	$C_9H_{10}O$	134.175	$C_9H_{10}O$	134.175	—	—

* g/mole

In a substitution reaction, one atom (or group of atoms) is replaced by another atom (or group of atoms). Because the

TABLE 2

Reagent		Utilized		Unutilized	
Formula	FW*	Formula	FW*	Formula	FW*
1 C_3H_6	42.080	C_3H_6	42.080	–	–
2 H_2	2.016	H_2	2.016	–	–
Total					
C_3H_8	44.096	C_3H_8	44.096	–	–

* g/mole

TABLE 3

Reagent		Utilized		Unutilized	
Formula	FW*	Formula	FW*	Formula	FW*
1 $C_5H_{10}O_2$	102.132	C_3H_5O	57.057	C_2H_5O	45.061
2 CH_5N	31.057	CH_4N	30.049	H	1.008
Total					
$C_6H_{15}NO_2$	133.189	C_4H_9NO	87.120	C_2H_6O	46.069

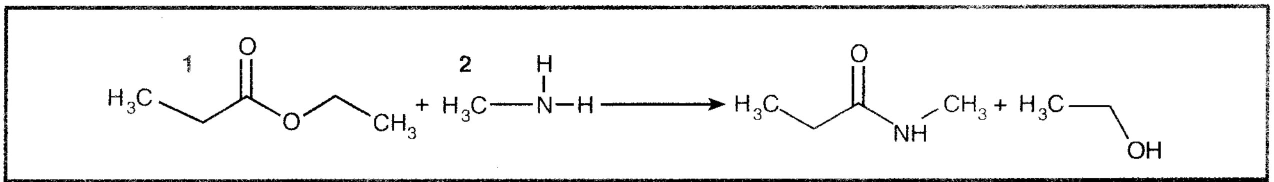
* g/mole

atom that is replaced is not utilized in the final desired product, the substitution reaction is less atom-economical than rearrangements or additions.[7] An example of a substitution reaction is the reaction of ethyl propionate with methyl amine (Scheme 3).

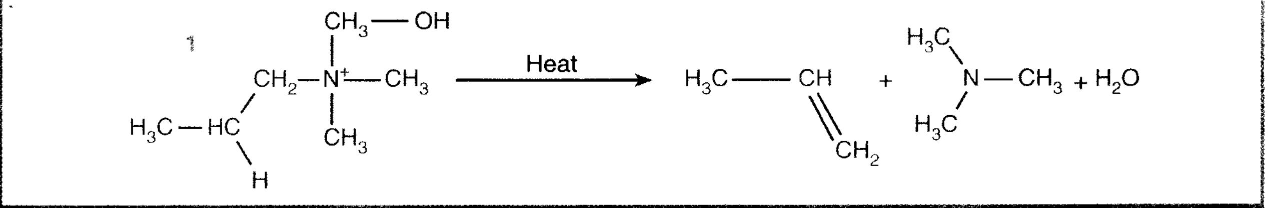
Note that in this reaction, the leaving group (OCH_2CH_3) (highlighted in brown) is not utilized in the desired amide product. In addition, one hydrogen atom on the amine is not utilized (also highlighted in brown). The remaining atoms in the reactants are incorporated into the final product (highlighted in green). The total of the atomic weights of the atoms in the reactants that were used (Table 3, column 2, bottom row) is 87.120 g/mole, while the total molecular weight of the reagents used (Table 3, column 1, bottom row) is 133.189 g/mole. Thus, a molecular weight of 46.069 g/mole remains unutilized in this reaction (Table 3, column 3, bottom row). The percentage atom economy for this reaction is 65.41% (87.120/133.189 × 100 = 65.41%).

In a typical elimination reaction, two atoms or groups of atoms are lost from the reactant to form a π bond. The elimination reaction is not very atom-economical, as the two groups that are lost from the reactant are not found in the final desired product.[7] An example of such a reaction is the Hofmann elimination (Scheme 4).

In this reaction, only three carbon and six hydrogen atoms (highlighted in green) are utilized in the formation of propene. The rest of the atoms remain unutilized (highlighted in brown). The total of the atomic weights of all the atoms in the reagents that are utilized in the final product is 42.080 g/mole (Table 4, column



SCHEME 3



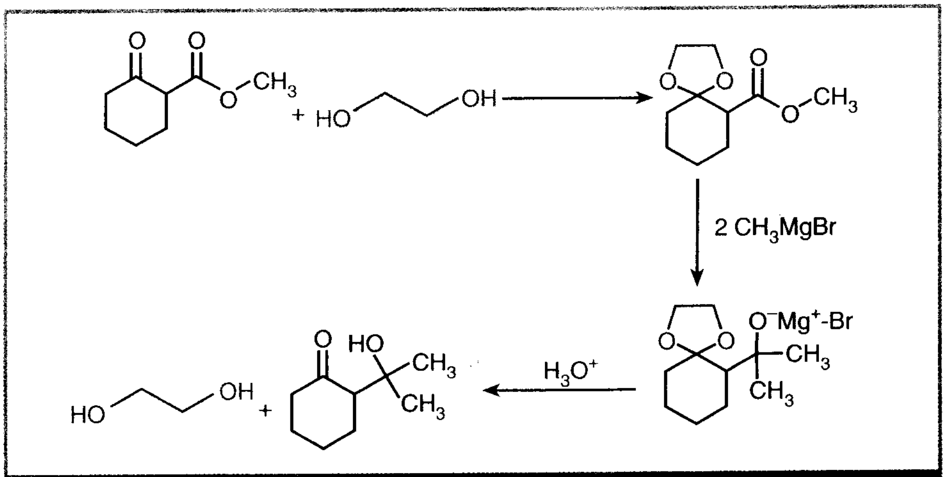
SCHEME 4

2, bottom row), while the total formula weight of all the reagents used in the reaction is 119.205 g/mole (Table 4, column 1, bottom row). This means that 77.125 g/mole of the reactants were not utilized in this reaction (Table 4, column 3, bottom row). By dividing the formula weight of the atoms utilized by the total formula weight of all the reactants used and multiplying by 100 (Formula 3), the percentage atom economy is a low 35.30% (42.080/ 119.205 × 100 = 35.30%).

TABLE 4

	Reagent		**Utilized**		**Unutilized**	
	Formula	**FW***	**Formula**	**FW***	**Formula**	**FW***
1	$C_6H_{17}NO$	119.205	C_3H_6	42.080	$C_3H_{11}NO$	77.125
Total						
	$C_6H_{17}NO$	119.205	C_3H_6	42.080	$C_3H_{11}NO$	77.125

* g/mole



SCHEME 5

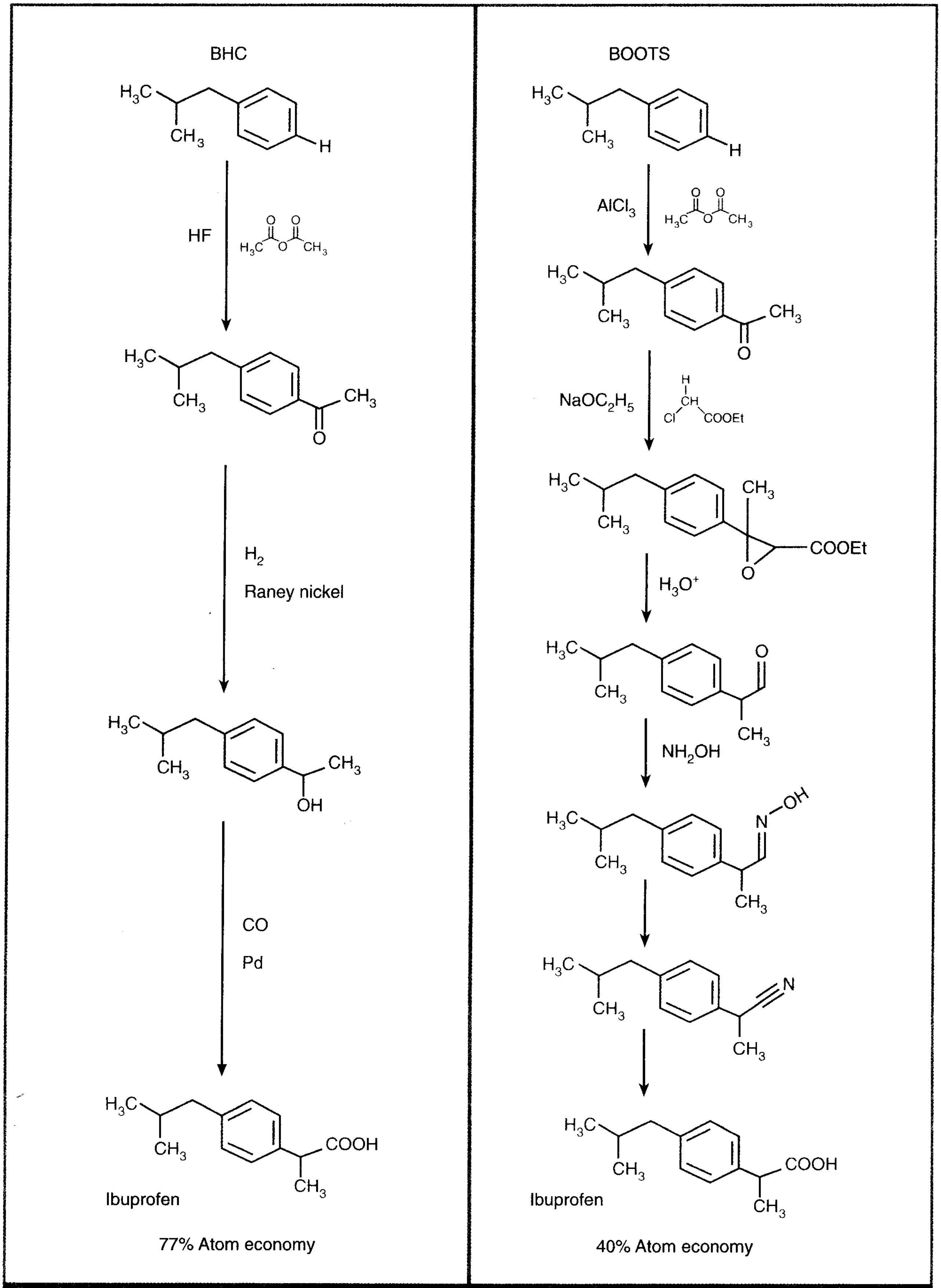
In addition to these four reaction pathways playing a role in atom economy, the use of protecting groups (blocking groups) can also be a factor in the atom economy of a reaction.[4,12] Although protecting groups are sometimes needed to solve a chemoselectivity problem, they usually need to be added to the reaction in stoichiometric amounts and then removed after the reaction is complete. Because these protecting groups are not incorporated into the final product, their use can make a reaction less atom-economical. An example of such a protecting group is the use of 1,2-ethanediol to protect a keto group from reacting with a Grignard reagent (Scheme 5). Notice that the protecting group (highlighted in brown) in this reaction is not utilized in the final product. Therefore, its use makes the reaction less atom-economical.

While atom economy is a very valuable tool in evaluating how efficiently starting materials are used in a reaction or synthesis, other aspects of efficiency must be considered if we are going to call a reaction "green." In addition to atom economy, one should also consider:

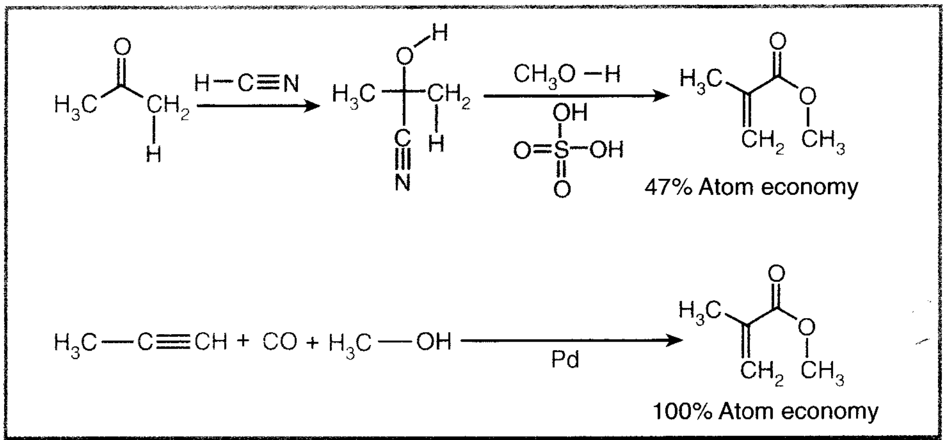
- **The nature of the waste produced: Is the waste toxic or environmentally harmful?**
- **The amount of energy needed to make the reaction proceed: Does the reaction require excessive amounts of energy?**
- **The use of auxiliary reagents: Does the synthesis require solvents or the use of significant amounts of materials to extract and/or purify the product?**
- **The percent yield of the reaction: Is a high yield of the product obtained or is most of the material lost as waste?**
- **The selectivity of the reaction: Is the reaction chemoselective, regioselective, enantioselective, and diastereoselective?**

Green Chemistry in Action

Trost has developed many atom-economical reactions using various transition metals as catalysts.[2,8] In addition, various companies have used the concept of atom economy to develop new syntheses that employ a more atom-economical use of reactants. One such company is BHC (a joint venture between BASF and Hoechst Celanese), which has developed a more



SCHEME 6. Synthesis of Ibuprofen



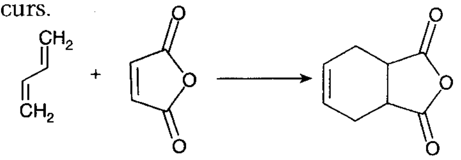
SCHEME 7

atom-economical way to manufacture ibuprofen[6] (the active ingredient used in drugs such as Advil and Motrin). (See the green chemistry case on the BHC Company Ibuprofen Process.) From a cursory glance, one can see that the new BHC synthesis (Scheme 6, left side) uses far more of the reactant atoms (highlighted in green; unutilized atoms are highlighted in brown) than the Boots synthesis (Scheme 6, right side). In fact, the BHC synthesis results in 77% atom economy, a significant improvement over the 40% atom economy found in the older Boots synthesis (Scheme 6, right side).[6]

Another example of atom economy is displayed in a synthesis developed by the Shell Corporation to make methyl methacrylate[6] (the monomer used to make the clear polymer known by the trade names Plexiglas and Lucite). The old synthesis (Scheme 7, top) has 47% atom economy due to the use of stoichiometric amounts of hydrogen cyanide and sulfuric acid.[6] The new synthesis, which employs a palladium catalyst (Scheme 7, bottom), enjoys 100% atom economy.[6]

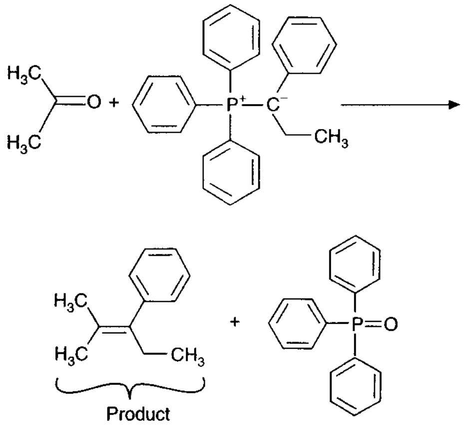
QUESTIONS

1. Why might the primary concern of specialty chemicals and pharmaceuticals be selectivity?
2. What are chemoselectivity, regioselectivity, enantioselectivity, and diastereoselectivity?
3. What types of reactions are ideal in terms of atom economy (consider the addition, rearrangement, substitution, and elimination reactions)?
4. Supply a mechanism for the Claisen rearrangement (Scheme 1).
5. Supply a mechanism for the catalytic hydrogenation of propene (Scheme 2).
6. Supply a mechanism for the acyl substitution reaction of ethyl propionate with an amine as the nucleophile (Scheme 3). Which atoms are unutilized in this reaction?
7. Supply a mechanism for the Hofmann elimination (Scheme 4). Which atoms are unutilized in this reaction?
8. Propose a synthesis for propene that has better atom economy than the Hofmann elimination in Scheme 4.
9. If the protecting group were not used in the reaction shown in Scheme 5, what would the product(s) of this reaction be?
10. Why do protecting groups reduce the atom economy of a reaction?
11. In addition to atom economy, what other aspects of a synthesis need to be considered before one can call the synthesis "green"?
12. Indicate how the Diels–Alder reaction shown below occurs.



Calculate the percentage atom economy of this reaction. Is this an atom-economical reaction?

13. The Wittig reaction can be used to make alkenes. An example of such a reaction is shown below.



Sketch the mechanism of this reaction. Which atoms are utilized in the final product? Which atoms are not utilized in the product? What is the percentage atom economy of this reaction? Is this an atom-economical reaction?

14. "The Concept of Atom Economy" won a Presidential Green Chemistry Challenge Award in 1998. Look up the three focus areas for the Presidential Green Chemistry Challenge (download the *Presidential Green Chemistry Challenge Brochure* at **http://epa.gov/greenchemistry/presgcc.htm**; accessed Dec 1999) and decide which focus area (or areas) this case study best fits.
15. Following the Twelve Principles of Green Chemistry (see inside front cover) can lead to more environmentally benign technologies.[7] Which principle(s) are used in "The Concept of Atom Economy"?

REFERENCES AND NOTES

1. This case is based on the work of Barry M. Frost, Department of Chemistry, Stanford University, who received a 1998 award in the Presidential Green Chemistry Challege Awards Program. For more information on the Awards Program, please visit the program Web site at **www.epa.gov/greenchemistry** (accessed Dec 1999) or contact the U.S. EPA Green Chemistry Program at 202-260-2659.
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11. This is a term coined by the authors of this book.
12. *Green Chemistry: Designing Chemistry for the Environment;* Anastas, Paul T., Williamson, Tracy C., Eds.; ACS Symposium Series 626; American Chemical Society: Washington, DC, 1996.