

to account for the contribution of anisotropy to wave speed.

Cai *et al.* report that more than four times as much water is entering the Mariana subduction zone than was previously estimated⁹. Old, cold subducting plates such as that entering the Mariana Trench are particularly effective conveyors of water into the deep Earth because hydrous minerals in such plates are stable to greater depths than in younger, hotter plates. If extrapolated globally to other places where old, cold plates subduct, the authors' result implies that the amount of water entering Earth's interior greatly exceeds current estimates¹⁰ of the amount being emitted by volcanoes, and thus requires a rethink of the global water budget.

Several questions still need to be answered to better constrain estimates of the inputs to Earth's deep-water cycle and evaluate the implications of the new results. First, how variable is the water content in the oceanic plate at a range of depths and scale lengths along subduction zones? Many studies have reported changes in extensional faulting and in crustal and upper-mantle hydration along subduction zones, and several competing factors have been proposed to contribute to these changes^{7,11,12}. Characterizing this variability throughout the hydrated part of the plate and understanding its causes will be essential for us to tally water inputs and compare them with outputs. It would also be useful to determine whether hydration occurs in focused zones near faults, as has been observed in a different tectonic setting¹³, or is distributed more evenly, because this might control whether mineral-bound water is released by dehydration or is carried to greater depths¹⁴.

Finally, because a substantial volume of water is probably stored in the crust and upper mantle (the regions that are most accessible to seawater infiltration), the thorny issue of whether changes to seismic waves reflect the presence of water-filled cracks or of hydrous minerals still needs to be directly addressed in these areas. A comprehensive understanding of inputs to Earth's interior will require a multi-pronged approach, including multi-scale marine geophysical studies, drilling of the faults that are thought to be conduits for water into the oceanic lithosphere, and numerical and laboratory studies. But for now, Cai and colleagues' results have taken us a big step closer to understanding the total water input at subduction zones. ■

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ORGANIC CHEMISTRY

From hydrocarbons to precious chemicals

Operationally simple chemistry enables aliphatic carbon–carbon bonds — the ‘girders’ in the framework of many organic molecules — to be prepared from widely available hydrocarbons known as alkenes. SEE LETTER P.379

JAMES P. MORKEN

Many valued reagents and catalysts used in the preparation of organic compounds are highly reactive and are therefore incompatible with exposure to the open atmosphere — in some cases, dangerously so. The instrumentation required to carry out reactions with these compounds, such as high-vacuum apparatus and gloveboxes (isolation chambers), is costly and demands special training. Chemical processes that do not have such requirements are therefore more likely to make a big impact on how chemists synthesize molecules, be it for the development of new

materials, pharmaceuticals or agrochemicals. The reactions reported by Fu and co-workers¹ on page 379 are a case in point. Not only are they simple to carry out, but they also deliver a variety of useful products that are otherwise much more difficult to make.

Parallels are often drawn between the fields of organic synthesis and architecture²: aliphatic carbon–carbon (C–C) bonds are the architect's ‘girders’ on which many structurally complex molecules are built. Installing these girders is challenging, and necessitates the use of highly reactive reagents. To add to the challenge, the orientation in which new C–C bonds are installed — the stereochemistry of

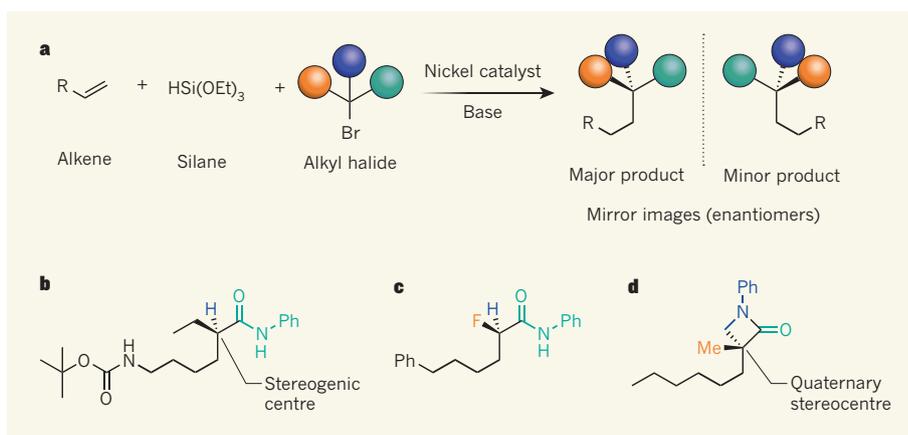


Figure 1 | Operationally simple reactions for making aliphatic carbon–carbon bonds. **a**, Fu and colleagues¹ report chemistry in which an alkene, a silane and an alkyl halide react in the presence of a nickel catalyst and a base to form potentially useful products. The reactions can be carried out without excluding air or moisture, which makes them straightforward in practice. Moreover, the reactions are enantioselective: they produce one isomer of the reaction product to the near exclusion of the product's mirror-image isomer. R and the coloured spheres represent a variety of organic groups or atoms; Si, silicon; Et, ethyl group; Br, bromine. **b–d**, The authors prepared a variety of products, including **b**, compounds in which a stereogenic centre (a carbon atom that has three other groups attached by carbon atoms) is next to a carbonyl group (C=O); **c**, compounds that contain fluorine atoms; and **d**, compounds that contain quaternary stereocentres (carbon atoms attached to four different groups by carbon atoms). Ph, phenyl group; Me, methyl group.

the reaction — affects the overall shape of the final molecule³, which in turn can affect the molecule's function in applications.

Fu and colleagues' advance addresses these challenges. The authors describe a new C–C bond-forming reaction, known as a cross-coupling reaction, that produces one isomer of the reaction product to the near exclusion of the product's mirror-image isomer (in chemists' terms, the reaction is said to be enantioselective). Moreover, the process does not require the use of highly reactive and fragile reagents.

The authors' approach requires three reagents: an alkene, a silane and an alkyl halide (Fig. 1a). Alkenes are not sensitive to air, which distinguishes Fu and colleagues' reactions from the majority of cross-coupling reactions⁴, in which the alkene is replaced by an air-sensitive organometallic compound, either as a reagent or as the precursor to a reagent. The new reactions seem to involve an orchestrated set of events wherein the alkene first attaches to a catalytic nickel complex, which is generated *in situ* by a process that involves the silane reagent. The attachment of the alkene produces a transient reactive species, which then reacts with the alkyl halide to form the new C–C bond.

Fu and co-workers' nickel-catalysed process is related to one reported⁵ by another team in 2016, but enhances the usefulness of that approach by addressing two key challenges. First, a catalyst had to be identified that not only promotes stereoselective C–C bond formation for an array of different substrates, but also activates the alkene without promoting side reactions between the silane and either the alkyl halide or the alkene. Second, reaction conditions had to be identified that allowed a base to drive catalytic cycles — which is difficult in this context, because bases often interconvert mirror-image isomers.

Not only is the use of alkenes as replacements for reactive organometallic reagents appealing in terms of its practical simplicity, but it also broadens the range of substrates that can be used in Fu and colleagues' reactions. Alkenes are widely available, many are produced industrially on a large scale, and they can be generated by a variety of chemical processes. Alkenes are also especially attractive as reagents for chemical synthesis: they are chemically inert to a range of reagents, but can be induced to react in the presence of the right catalyst and under the right set of conditions. Impressively, the catalytic conditions used by the authors allow alkenes to react without interference when a variety of other common organic groups are also attached to the alkene (see Fig. 2a of the paper¹).

Intriguingly, when Fu and colleagues used internal alkenes — in which the characteristic carbon–carbon double bond of the alkene is in the middle of a chain of carbon atoms — in their reactions, they observed a phenomenon called chain-walking⁶, which causes the double

bond to migrate to the end of the carbon chain before reacting. This observation means that products obtained from an increasingly used type of reaction known as olefin cross-meta-thesis⁷ (which produces internal alkenes) might be suitable substrates. It will also be exciting to find out whether the step in which the alkene attaches to the nickel complex can be made to be enantioselective, because this would allow products containing multiple stereogenic centres (carbon atoms to which three different groups are attached by carbon atoms) to be generated enantioselectively.

A particularly notable feature of Fu and co-workers' strategy is that a considerable array of alkyl halides can be used, some of which are not effective substrates for cross-coupling reactions with organometallic reagents. For example, the authors use alkyl halides known as secondary α -halo amides in their reactions, and show that this provides a simple and enantioselective route to prepare compounds that contain a carbonyl (C=O) group next to a stereogenic centre (Fig. 1b). Such compounds are potentially versatile intermediates for chemical synthesis, and have most commonly been prepared using a much less efficient approach based on the use of compounds called chiral auxiliaries⁸. The researchers also demonstrate that they can use their enantioselective reactions to make certain fluorine-containing compounds (see Fig. 1c, for example), which might be useful in

medicinal chemistry. Moreover, the chemistry can be used to make compounds that contain quaternary stereocentres (Fig. 1d) — carbon atoms to which four different groups are attached by carbon atoms, which are some of the most difficult structures to prepare enantioselectively.

Overall, this advance is a much-needed method for the enantioselective synthesis of an impressive assortment of versatile small organic molecules, many of which will be of value to research at the frontiers of chemistry. ■

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HUMAN DEVELOPMENT

The landscape of early pregnancy

RNA sequencing of thousands of single cells located at the interface between mother and fetus in early pregnancy reveals remarkable complexity in the cell types and regulatory networks that support reproduction. [SEE ARTICLE P.347](#)

SUMATI RAJAGOPALAN & ERIC O. LONG

Scientists have long puzzled over the 'immunological paradox' of pregnancy¹: how does the mother tolerate the fetus — a foreign entity that carries some of the father's DNA? On page 347, Vento-Tormo *et al.*² investigate this enigma. The authors performed single-cell RNA sequencing (scRNAseq) of cells isolated from the placenta and the decidua (the lining of the pregnant uterus), and from matching maternal blood for comparison. They identified an array of cell types unique to this maternal–fetal interface, and inferred the existence of a large network of potential interactions between them that would favour immunological tolerance and nurture the

growth of the fetus. The authors' molecular atlas provides an impressive resource for future studies of pregnancy and its complications.

The early embryo develops into a structure called the blastocyst, which implants in the lining of the uterus. Implantation triggers the development of the placenta from fetal membranes. The placenta nourishes the fetus through the umbilical cord³. Abnormal placental development can lead to several complications of pregnancy, including pre-eclampsia, fetal growth restriction and stillbirth. A better understanding of human placental development is sorely needed, but there is no good animal model for this process — it has to be studied in women.

Vento-Tormo *et al.* collected placental,