C–C Coupling Reactions

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Heterodimerization of Olefins: A Highly Promising Strategy for the Selective Synthesis of Functionalized Alkenes

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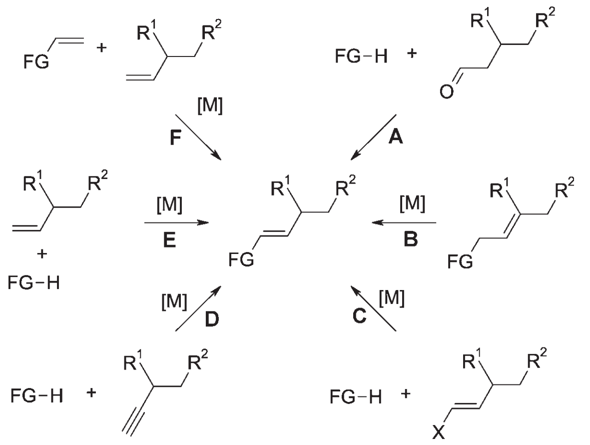
alkenes · catalysis · enamides · heterodimerization · ruthenium

Enamides, enol esters, α,β-unsaturated carbonyl compounds, vinyl halides, vinyl boronic acids—these are just a few examples of alkenes that carry an additional functionality directly attached to the double bond. Such substructures are found both in pharmaceutically active compounds (for example, enamides in the active antitumor agents lobatamide[1] and salicylihalamide[2] or 2-alkylidenetetrahydrofurans in macrotetrolide antibiotics[3]) and in functional materials such as polyvinylpyrrolidone derivates.[4] In addition, they are versatile synthetic intermediates for Diels–Alder reactions,[5] polymerizations,[6] cycloadditions,[7] cross-coupling reactions,[8] Heck reactions,[9] enantioselective additions,[10] and asymmetric hydrogenations.[11]

Scheme 1 gives an overview of the existing routes to such compounds. In classical syntheses, aldehydes or ketones are condensed with proton-active compounds such as alcohols, amides, carboxylic acids, malonic acid derivatives, or alkyl phosphonium halides (Route **A**).[12] The disadvantage here is that the products are obtained mostly as *E*/*Z* mixtures. Another route is the isomerization of a double bond into the desired position (Route **B**).[13]



Scheme 1. Alternative syntheses of functionalized alkenes. FG = functional group.

Syntheses by catalytic functionalization of vinyl halides, such as cross-coupling reactions with amides or carbonylation, are inherently regio- and stereoselective, but are limited by the availability of the vinyl halides (Route **C**).[14] An atom-economic route is provided by the catalytic addition of O-H, N-H, P-H, S-H, or C-H compounds to C≡C triple bonds, but only if the regio- and stereoselectivities are defined by the catalysts used, such as in the Ru-catalyzed synthesis of enamides (Route **D**).[15] The oxidative functionalization of alkenes is a further modern preparative technique for enamides and enol esters (Route **E**).[16] Versatile perspectives are also provided by the application of alkene cross-metathesis. By joining two different terminal olefins under release of ethane, a disubstituted alkene is produced (Route **F**).[17] This approach can even be applied to highly functionalized derivatives such as vinyl phosphonate coupled nucleotide dimers,[18] although control of the *E*/*Z* selectivity is thus far limited.

A new synthetic strategy is currently emerging as an alternative to these methods, which are all limited in one way or another: the Ru-catalyzed dimerization of two different olefins.[19,20] The recently published initial examples were surprising insofar as a successful selective heterodimerization of two alkenes requires that the homodimerization of each reaction partner is effectively suppressed and oligomerizations essentially do not occur. A special case for this has been known for some time, the Ni-catalyzed codimerization of alkenes with ethene, which is used preparatively in hydrovinylations.[21] In 2005 Mitsudo and co-workers demonstrated that selective heterodimerization can also be achieved successfully with alkenes other than ethene: in the presence of a Ru catalyst generated in situ from [$RuCl_3$(tpy)] (tpy = terpyridyl) and zinc dust they treated norbornene derivatives with acrylate esters and obtained mainly *trans*-configured heterodimers (Scheme 2).[19] Unlike in the case of Ni-catalyzed hydrovinylations, linear products were formed preferably in this Ru-mediated reaction.

The new reaction principle initially attracted little attention since it appeared to be restricted to very special substrates. Recently, however, Ura, Kondo et al. were able

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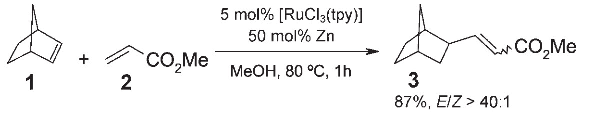
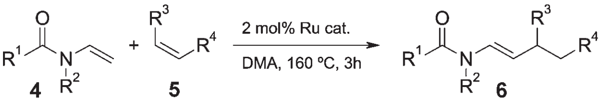


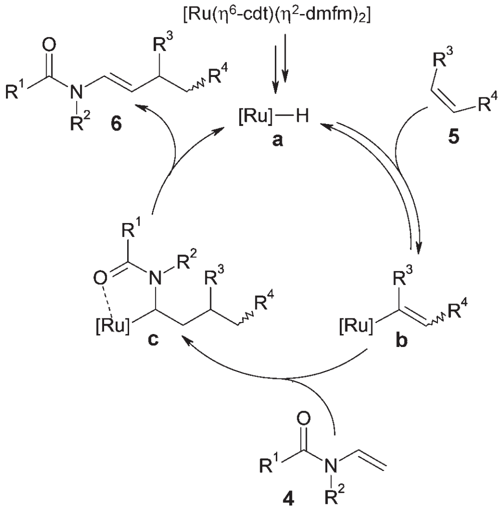
Scheme 2. An early example of an olefin heterodimerization.

to extend the method to the important class enamides (Scheme 3). They treated *N*-vinyl amides with other different olefins to form *E*-configured, linear enamides in moderate yields and with good stereoselectivities.[20] A particular advantage with respect to their use in synthesis is that unlike more complex enamides, *N*-vinyl amides are readily available since they are used industrially as monomers for (co)polymerizations.



Scheme 3. Heterodimerization of *N*-vinyl amides with olefins.

Mechanistic investigations including deuteration studies and the crystallization of intermediates have already allowed a number of conclusions on the catalytic cycle to be reached (Scheme 4). Bis(η^2-dimethyl fumarate)(η^6-1,3,5-cyclododecatriene)ruthenium(0) ([Ru(η^6-cdt)(η^2-dmfm)$_2$]) was used as a precatalyst, which after addition of an amide to the cyclododecatriene ligand and sp^2-C-H activation is transformed into a coordinatively unsaturated ruthenium hydride species. In the postulated catalytic cycle, reversible insertion of the alkene into the Ru–H bond initially takes place, followed by a chelation-supported insertion of the *N*-vinyl amide into the Ru–C bond. Finally the chain-extended enamide is released by β-hydride elimination and the original Ru–H species is regenerated. Alternative catalytic cycles via ruthenacyclopentanes are also conceivable, but appear less likely from deuterium studies.



Scheme 4. Postulated catalytic cycle.

The new reaction has been used successfully for combinations of secondary enamides with ethene, norbornene, acrylates, fumarates, and vinylketones. Selected results are collated in Figure 1.

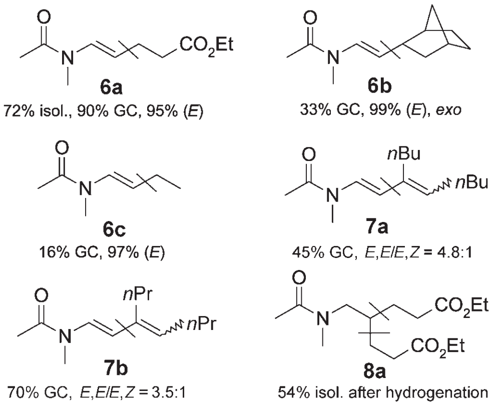


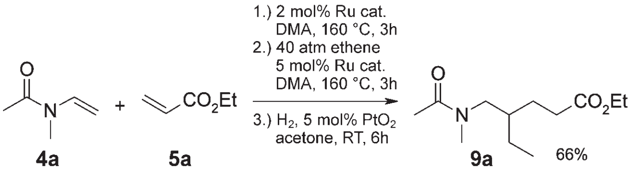
Figure 1. Examples of the application of heterodimerization.

The examples suggest a considerable potential for the reaction, although the products could not always be isolated in good yields, and there are also limitations with respect to the reaction temperature and substrate spectrum: the enamide components in particular can currently be modified only marginally since the chelating coordination of this substrate to the catalyst, which is pivotal for the mechanism, appears to be susceptible to even small structural modifications.

The new catalyst is not only applicable to the codimerization of vinyl amides with alkenes (Figure 1, **6a**–**c**), but it also mediates the analogous reaction of vinyl amides with alkynes to form dienamides (**7a**, **7b**). However, in view of the many efficient codimerizations of alkenes with alkynes[22] this reaction variant is rather less spectacular.

In the heterodimerization of enamides with other alkenes, the product is clearly also an enamide, and can itself act as a substrate for heterodimerization. This potential side reaction only plays a subordinate role when an equimolar ratio of both substrates is used, but if the reaction partner is used in excess, two molecules are incorporated selectively. A 2,2-disubstituted enamide is formed whose isomers were transformed by hydrogenation into a single compound and subsequently characterized (Figure 1, **8a**). With suitable reaction control, even three different alkenes can be selectively coupled: Two sequential heterodimerizations—first of vinyl amide **4a** and acrylate **5a** to form **6a**, which subsequentially reacts further with ethene—provides the cotrimer as an isomeric mixture, which is converted into a single product **9a** by hydrogenation (Scheme 5). This is the first example of a selective cotrimerization of three different alkenes, even if it occurs in two individual steps.

The work of Ura, Kondo et al. thus shows that selective codimerization and cotrimerization of enamides with other alkenes is possible. The underlying reaction principle of using different coordination modes at a metal catalyst to couple two



Scheme 5. "Cotrimerization" of three different alkenes **4a**, **5a**, and ethene.

olefins with one another offers significant synthetic potential. Although there is room for improvements in terms of yield and substrate spectrum, the reaction described could be groundbreaking for the development of new, atom-economic pathways to other functionalized alkenes such as enol esters, vinyl ethers, or α,β-unsaturated carbonyl compounds. Initial follow-up work appears to confirm this assessment.[23]

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[1] L. Yet, *Chem. Rev.* **2003**, *103*, 4283–4306.

[2] R. Shen, C. T. Lin, E. J. Bowman, B. J. Bowman, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2003**, *125*, 7889–7901.

[3] G. Solladié, C. Domínguez, *J. Org. Chem.* **1994**, *59*, 3898–3901.

[4] H.-G. Elias, *Makromoleküle, Industrielle Polymere und Synthesen*, vol. 3, Wiley-VCH, Weinheim, **2001**, p. 207–211.

[5] a) Y. Tsuda, K. Isobe, A. Ukai, *Chem. Commun.* **1971**, 1554–1555; b) W. Oppolzer, W. Frostl, *Helv. Chim. Acta* **1975**, *58*, 590–593; c) T. Yasukouchi, K. Kanematsu, *J. Chem. Soc. Chem. Commun.* **1989**, 953–954.

[6] "*N*-Vinylamide polymers": D. H. Lorenz, *Encycl. Polym. Sci. Technol.* **1971**, *14*, 239–251.

[7] a) A. R. Katritzky, B. Rachwal, S. Rachwal, *J. Org. Chem.* **1995**, *60*, 3993–4001; b) C. A. Zezza, M. B. Smith, *J. Org. Chem.* **1988**, *53*, 1161–1167; c) L. E. Overman, L. A. Clizbe, *J. Am. Chem. Soc.* **1976**, *98*, 2352–2354.

[8] G. J. Roff, R. C. Lloyd, N. J. Turner, *J. Am. Chem. Soc.* **2004**, *126*, 4098–4099.

[9] C. E. Willans, C. A. Mulder, J. G. de Vries, H. M. de Vries, *J. Organomet. Chem.* **2003**, *687*, 494–497.

[10] R. Matsubara, Y. Nakamura, S. Kobayashi, *Angew. Chem.* **2004**, *116*, 1711–1713; *Angew. Chem. Int. Ed.* **2004**, *43*, 1679–1681.

[11] T. Sell, A. Meiswinkel, G. Mehler, M. T. Reetz, *Tetrahedron Lett.* **2002**, *43*, 7941–7943.

[12] a) A. Couture, E. Deniau, P. Grandclaudon, *Tetrahedron Lett.* **1993**, *34*, 1479–1482; b) P. Dupau, P. Le Gendre, C. Bruneau, P. H. Dixneauf, *Synlett* **1999**, 1832–1834.

[13] a) J. K. Stille, Y. Becker, *J. Org. Chem.* **1995**, *60*, 2139–2145; b) S. Sergeyev, M. Hesse, *Synlett* **2002**, 1313–1317; c) S. Krompiec, M. Pigulla, M. Krompiec, S. Baj, J. Mrowiec-Białónb, J. Kasperczykc, *Tetrahedron Lett.* **2004**, *45*, 5257–5261.

[14] Reviews on Pd-mediated coupling reactions: a) J. R. Dehli, J. Legros, C. Bolm, *Chem. Commun.* **2005**, 973–986; examples of Cu-mediated coupling reactions: b) T. Ogawa, T. Kiji, K. Hayami, H. Suzuki, *Chem. Lett.* **1991**, 1443–1446; c) L. Jiang, G. E. Job, A. Klapars, S. L. Buchwald, *Org. Lett.* **2003**, *5*, 3667–3669.

[15] L. J. Gooßen, J. E. Rauhaus, G. Deng, *Angew. Chem.* **2005**, *117*, 4110–4113; *Angew. Chem. Int. Ed.* **2005**, *44*, 4042–4045.

[16] a) T. Hosokawa, M. Takano, Y. Kuroki, S.-I. Murahashi, *Tetrahedron Lett.* **1992**, *33*, 6643–6646; b) V. I. Timokhin, S. S. Stahl, *J. Am. Chem. Soc.* **2005**, *127*, 17888–17893; c) J. M. Lee, D.-S. Ahn, D. Y. Jung, J. Lee, Y. Do, S. Kim, S. Chang, *J. Am. Chem. Soc.* **2006**, *128*, 12954–12962.

[17] Review of cross-metatheses: S. J. Connon, S. Blechert, *Angew. Chem.* **2003**, *115*, 1944–1968; *Angew. Chem. Int. Ed.* **2003**, *42*, 1900–1923.

[18] M. Lera, C. J. Hayes, *Org. Lett.* **2001**, *3*, 2765–2768.

[19] H. Tsujita, Y. Ura, S. Matsuki, K. Wada, T. Mitsudo, T. Kondo, *Angew. Chem.* **2007**, *119*, 5252–5255; *Angew. Chem. Int. Ed.* **2007**, *46*, 5160–5163.

[20] Y. Ura, H. Tsujita, K. Wada, T. Kondo, T. Mitsudo, *J. Org. Chem.* **2005**, *70*, 6623–6628.

[21] a) P. W. Jolly, G. Wilke in *Applied Homogeneous Catalysis with Organometallic Compounds*, 2. ed., vol. 3 (Eds.: B. Cornils, W. A. Herrmann), Wiley-VCH, Weinheim, **2002**, p. 1164–1189; b) T. V. RajanBabu, *Chem. Rev.* **2003**, *103*, 2845–2860; c) L. J. Gooßen, *Angew. Chem.* **2002**, *114*, 3929–3932; *Angew. Chem. Int. Ed.* **2002**, *41*, 3775–3778.

[22] a) B. M. Trost, T. J. Müller, J. Martínez, *J. Am. Chem. Soc.* **1995**, *117*, 1888–1899; b) M. Murakami, M. Ubutaka, Y. Ito, *Tetrahedron Lett.* **1998**, *39*, 7361–7364.

[23] T. Kondo, D. Takagi, H. Tsujita, Y. Ura, K. Wada, T. Mitsudo, *Angew. Chem.* **2007**, *119*, 6062–6065; *Angew. Chem. Int. Ed.* **2007**, *46*, 5958–5961.