Dual Catalysis

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Combining the Concepts: Dual Catalysis with Carbophilic Lewis Acids**

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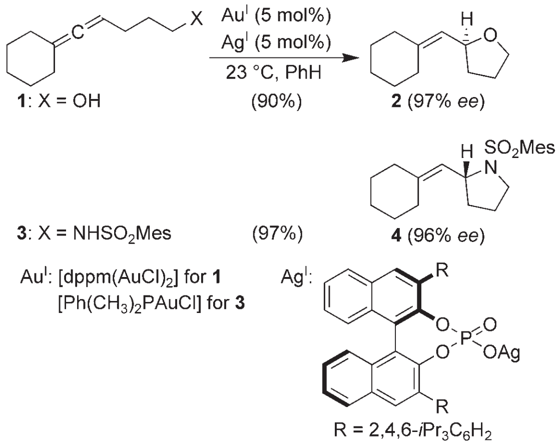
Noble-metal complexes acting as "π acids" (as defined by Fürstner and Davies)[1] are powerful tools for the formation of C–C and C–heteroatom bonds. In general, their synthetic value originates from initial complexation of C–C multiple bonds. As a result, the π system becomes activated toward intramolecular or intermolecular nucleophilic attack.[2] By the proper choice of substrates or reactants transformations can be orchestrated that generate products with a high degree of molecular complexity.[3] In these reactions the homogenous transition-metal catalyst assumes a role that goes far beyond that of a simple proton equivalent.[1,4]

Within the last decade, a number of experimentally convenient reactions have been developed that are initiated through the activation of C–C multiple bonds using carbophilic Lewis acids. In such transformations, the desired efficacy of noble-metal catalysts does not typically require the use of additives or cocatalysts. One exception is soluble silver salts; their addition may lead to an increase in reactivity by formation of cationic species through anion exchange (e.g., $[\mathrm{LAuX}] + \mathrm{Ag}^+ + \mathrm{Y}^- \rightarrow [\mathrm{LAu}]^+ + \mathrm{Y}^- + \mathrm{AgX}$). Although this type of activation is generally performed in situ, silver salts cannot be considered cocatalysts since the effect of the added silver salts mainly arises from the formation of insoluble silver halides. To determine the direct influence of the counterion on the reaction outcome remains rather difficult. In this context the asymmetric cyclization described by Toste and coworkers in 2007 is particularly remarkable (Scheme 1).[5] Therein, the concept of gold-catalyzed π activation was combined with a strategy employing chiral ion pairs to accomplish an asymmetric reaction. Unlike in classical metal catalysis where chiral ligands are bound to the metal center, the induction of asymmetry now exclusively depends on the chiral counterion.[6] In a seminal application, this concept was used to catalyze both the intramolecular hydroalkoxylation of allenes (**1**→**2**) and the corresponding hydroamination reaction (**3**→**4**) providing high yields and enantioselectivities. The cationic gold(I) catalyst was generated in situ from an achiral phosphine gold chloride and a chiral silver phosphate. As a solvent of low polarity, benzene proved to be suitable to achieve a high degree of enantioinduction. It seems likely that this concept can be extended to further reactions catalyzed by π acids. Moreover, the approach is certainly not restricted to the use of chiral phosphates as anions.



Scheme 1. Transition-metal catalysis with chiral anions. Mes = mesityl, dppm = $\mathrm{Ph_2PCH_2PPh_2}$.

Recently, an increasing number of strategies have been described that combine the now well-established concept of π activation by carbophilic Lewis acids[1–4] with other modes of catalysis. The idea is simple: By employing suitable cocatalysts in addition to a π acid, one may achieve reactivity not currently possible by use of the π-acid catalyst alone. In this context, it should be noted that this type of π acid should, in principle, be well-suited for use in combination with various organocatalysts and (transition-)metal complexes as co-catalysts owing to their inherent chemoselectivity towards C–C multiple bonds and their functional-group tolerance.[7]

One strategy combines electrophilic activation of π systems by coordination of transition-metal catalysts with nucleophilic activation by an appropriate organocatalyst. Thus, 1,2-dihydroisoquinolines such as **8** were prepared in a multicomponent reaction from 2-alkynyl benzaldehydes, primary amines, and enolizable ketones using AgOTf as the Lewis acid catalyst and proline as the Lewis base catalyst [Eq. (1) in Scheme 2].[8a] Catalytic activation of the carbonyl

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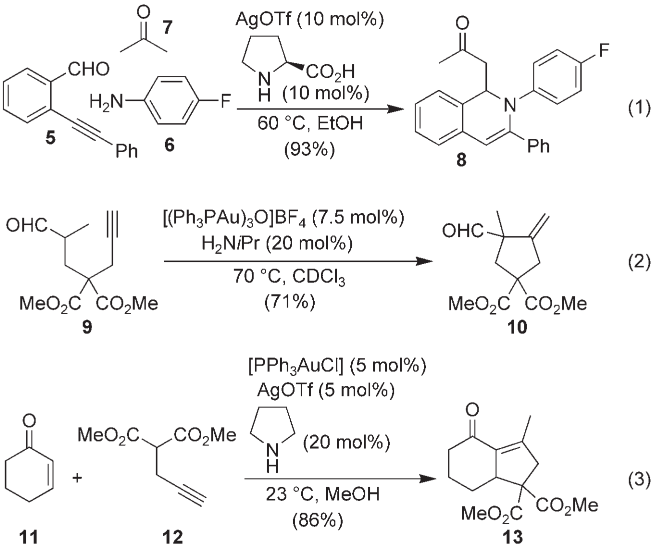
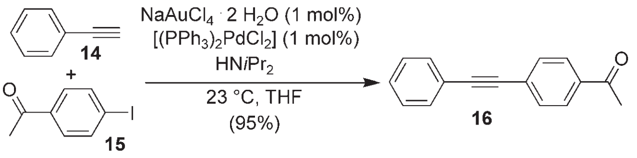


Scheme 2. Strategies combining π activation with enamine catalysis. Tf = trifluoromethanesulfonyl.

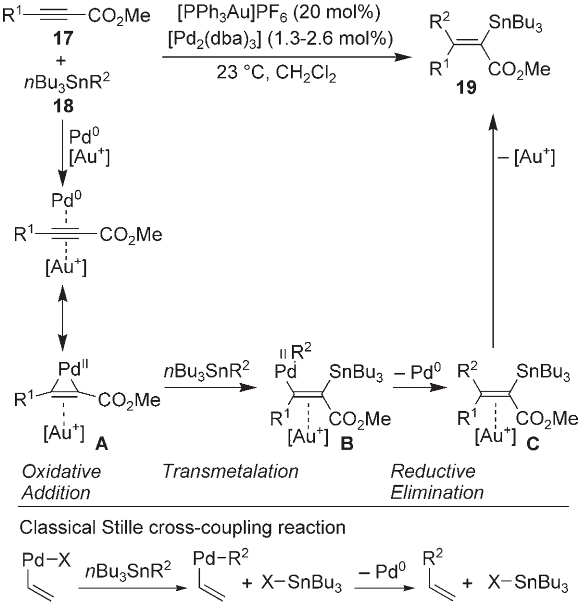
compound was expected to proceed following the principles of enamine catalysis. However, the exact role of proline (or other secondary amines) in this reaction remains unclear since the use of chiral organocatalysts consistently resulted in the formation of racemic products. A conceptually related approach enables the direct cyclization of formyl alkynes such as **9** by a combination of gold catalysis and enamine catalysis [Eq. (2) in Scheme 2].[8b] This reaction cascade can be extended by accessing the species required for cyclization directly from α,β-unsaturated ketones **11** and malonates **12** through an additional iminium-catalyzed step [Eq. (3) in Scheme 2].[8c] Whereas the reaction of unactivated alkynes with both preformed enol equivalents such as silyl enol ethers as well as with activated methylene compounds such as malonates and β-keto esters is directly catalyzed by π acids,[9] less enolizable carbonyl compounds (e.g., **9**→**10** and **11**→**13**) typically require an amine co-catalyst to ensure C–C bond formation. In these cases as well, cyclization has not been unequivocally proven to proceed by nucleophilic attack of a catalytically generated enamine onto the complexed alkyne. Alternatively, a gold enolate may be formed initially in the presence of the amine base. Despite the mechanistic ambiguities, the combination of classical transition-metal catalysis with concepts of organocatalysis holds great potential.[10] Particularly in connection with noble-metal complexes, which display exceptional chemoselectivity for π systems, a multitude of developments in the field can be expected.[11]

Only recently, gold complexes were shown to be valuable as co-catalysts for palladium-catalyzed couplings. Laguna and co-workers demonstrated that a variety of gold(I) and gold(III) complexes can replace the traditional copper-based co-catalyst employed in Sonogashira-type cross-coupling reactions of phenylacetylene with aryl halides (Scheme 3).[12] Though CuI was found to be superior to the gold co-catalysts when THF was used as the solvent, these studies indicate that the catalytically generated organogold compounds have tremendous potential as transmetalating agents in palladium-catalyzed coupling reactions that still remains largely unexplored.

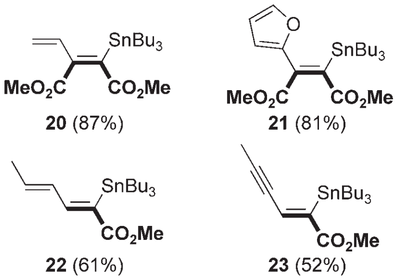


Scheme 3. Gold complexes as co-catalysts in Sonogashira cross-coupling reactions.

Blum and co-workers have developed a fascinating concept for a palladium-catalyzed Stille coupling not requiring organic halides as substrates (Scheme 4).[13] The halide as the partner for the oxidative-addition step is replaced by a simple alkyne which, after coordination of the gold co-catalyst, is activated for a nucleophilic addition by the palladium(0) species. It is assumed that the alkyne π system is transformed into a species **A** possessing palladium–carbon bonds with significant σ-bond character.[14] In the presence of vinylstannanes, transmetalation occurs leading to transfer of the vinyl group onto palladium while the tin fragment is transferred to the nascent olefin (formation of **B**). Product formation would then result from a subsequent reductive elimination. Although the mechanism discussed above must be regarded as hypothetical, this striking transformation demonstrates the unique reactivity attainable by means of a bimetallic catalyst system,[15] in this case a Pd^0 nucleophile and a Au^I Lewis acid. In the absence of either the gold complex or the palladium complex, formation of these highly substituted olefins was not observed. Less alkynophilic Lewis acid co-catalysts turned out to be markedly inferior to the cationic gold complex $[(Ph_3P)Au]^+$. The highly substituted olefins shown in Scheme 5 were obtained exclusively as the *syn-*



Scheme 4. Gold complexes as co-catalysts in Stille-type coupling reactions. dba = *trans,trans*-dibenzylideneacetone.



Scheme 5. Substituted olefins obtained in the Stille-type reaction described by Blum et al. The moiety stemming from the alkyne is in bold.

addition products. Furthermore, besides sp^2-hybridized stannanes also sp-hybridized stannanes were successfully employed. From a synthetic point of view, it is important to note that the vinylstannanes created in the course of the reaction do not react further under these conditions (presumably due to steric hindrance). Yet, under forcing conditions (5 mol% $[Pd_2(dba)_3]$, 20 mol% $P(2\text{-furyl})_3$, CuI, CsF, 1-methyl-2-pyrrolidinone), the crude product does undergo a subsequent Stille reaction with aryl iodides. It should be pointed out that so far only alkynes bearing at least one electron-withdrawing substituent have been employed in the reaction. Provided that the postulated mechanism is accurate in principle, one can hope that variation of the carbophilic Lewis acid and the nucleophilic palladium catalyst might also permit the use of donor-substituted acetylenes. Moreover, it will be interesting to see whether Blum and co-workers can subject such π systems activated by both Au^I and Pd^0 to other C–C bond-forming reactions as well. In this context, Suzuki couplings and Heck reactions appear to be particularly attractive for further functionalizations.

As the field of reactions catalyzed by noble-metal π acids rapidly evolves, it is worthwhile to look into other concepts of catalysis. Recently, a number of promising results have appeared that apply a classical π activation as part of a dual-catalysis concept through the combination with organocatalysis and particularly palladium catalysis. The reactions of this type described so far are certainly limited in number, and their mechanisms are not sufficiently understood to be considered generally applicable. Nevertheless, we expect that the coming years will see the ongoing development of novel strategies that utilize the beneficial properties of π acids and also require an additional catalytic component. Such combinations may lead to the discovery of fundamentally new reaction designs, as exemplified by the C–C bond formation developed by Blum and co-workers.

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