Dual Catalysis

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Copper/Palladium-Catalyzed 1,4 Reduction and Asymmetric Allylic Alkylation of α,β-Unsaturated Ketones: Enantioselective Dual Catalysis**

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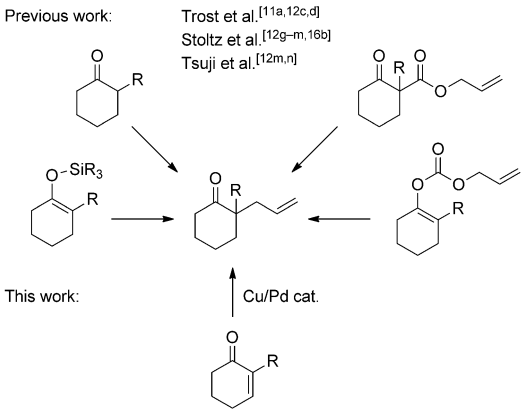
The development of new catalytic methods has been an area of intense research in recent years. It is becoming more and more vital to develop new concepts in catalysis that enable easy and reproducible access to products that are difficult to obtain otherwise. One of the ideas that have emerged most recently is the combination of two or more different catalysts in a single vessel to promote domino reactions.[1]

In most domino reactions, a single catalyst is used to promote two or more reactions in a specific order.[2] The significant drawback of this approach is the limited number of reaction types that a particular catalyst can promote. By combining two catalysts, the range of transformations that could be achieved is thus expanded.[3] Different types of dual catalysis have been reported recently, such as organocatalysis/metallocatalysis,[4] biocatalysis/metallocatalysis,[5] and metallocatalysis/metallocatalysis.[6] In the majority of examples in which two metal-based catalysts are used, the first metal generates the active species, which then undergoes the reaction and affords the desired product, whereas the second metal is present either to regenerate the active species of the first metal or for transmetalation, as is the case in the majority of C–C couplings.

The most interesting type of metal/metal catalysis is the cooperative dual catalysis.[6g,7] In this approach, the two catalysts separately and selectively activate two different substrates, thus catalytically generating two active intermediates that can subsequently react with each other to form the desired product. The formation of the final product is generally combined with the simultaneous regeneration of the catalysts. This type of dual catalysis is still underdeveloped, and only a few examples have been reported.[7] Another contributing factor is the possible reaction of intermediates with reagents that are present in stoichiometric amounts, thus resulting in side reactions and undesired products, and rendering the reaction very difficult to control.

Herein, we report a cooperative dual catalysis based on a palladium(0)/copper(I) system. Cooperative catalysis of palladium(0) and copper(I) is well documented, and the compatibility and selectivity of these two metals have been repeatedly proven in two famous examples: the Wacker–Tsuji[8] process and the Sonagashira coupling.[9]

Our group has a long history of developing copper(I) complexes and using them in domino reactions.[10] Our goal was to combine our experience in copper(I) catalysis and domino reactions with the palladium(0)-catalyzed asymmetric allylic alkylation.[11] To this end, we chose the copper(I)-catalyzed 1,4 reduction of α,β-unsaturated ketones and a robust and easy-to-handle copper(I) catalyst with an N-heterocyclic carbene (NHC) ligand.[10g] Several processes have been developed to access α-allylated ketones,[11a,12] this study however offers a new approach starting from easily available α,β-unsaturated ketones (Scheme 1).



Scheme 1. Different routes to access α-allylated ketones.[11a,12]

We chose commercially available D-(+)-carvone as a model substrate for our initial optimization reactions, thus allowing the formation of products that contain a quaternary center. Stereoselective access to these centers remains an important challenge in organic synthesis.[13] At first, the two reactions were conducted separately in order to determine the most compatible conditions. The first reaction is a 1,4 reduction of carvone by a preformed copper(I) hydride[14] to generate the silyl enolate in situ. This intermediate was then engaged, without further purification, in the palladium(0)-catalyzed asymmetric allylic alkylation reaction. Preliminary reactions were successful and allowed us to determine two compatible systems (Scheme 2).

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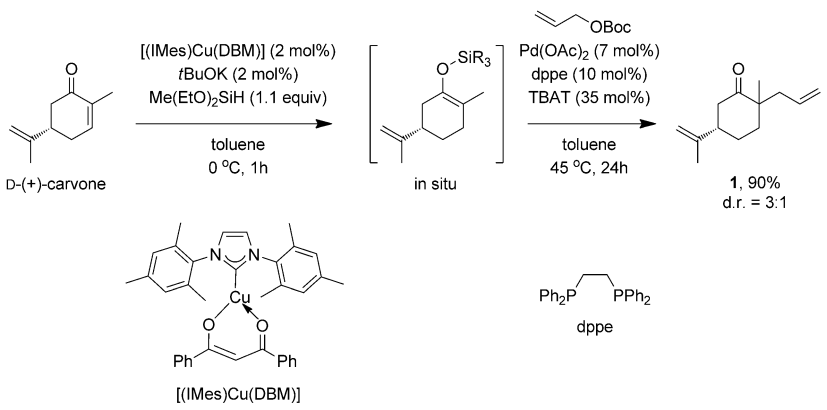
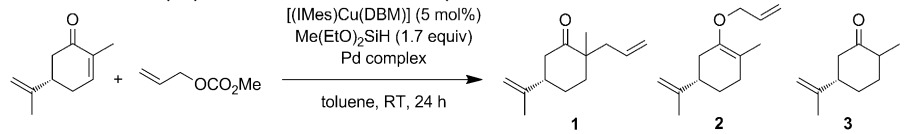


Scheme 2. Preliminary results. TBAT = tetrabutylammonium difluorotriphenylsilicate.

With these two systems at hand, the dual catalysis was investigated. Initial investigations allowed the observation of three products, the desired C-alkylation product **1**, the O-alkylation product **2**, and the reduction product **3** (Table 1). Different palladium sources led to significant variations of the ratio of the three products. The combination of $Pd(OAc)_2$ and dppe acted as the best catalyst in terms of overall conversion and yield of combined alkylated products **1** and **2** (Table 1, entry 4). Although $[Pd(PPh_3)_4]$ gives the best yield of C-alkylated product **1**, a lower overall conversion was observed (Table 1, entry 2). Nevertheless, a higher palladium loading results in lower yields of **1**, thus suggesting that tuning the Cu/Pd ratio could be essential to the minimization of secondary reactions (compare entries 1 and 2). No significant changes in diastereoselectivity of **1** were observed.

As predicted, the Cu/Pd ratio had a significant effect on the yield of alkylated products. A 5:1:2.5 ratio of Cu/Pd/dppe is necessary to obtain a maximum combined yield of **1** and **2** (Table 1, entry 4). We suspect that higher Pd loadings accelerate the consumption of the allylcarbonate in secondary reactions.

Table 1: Preliminary optimization of the dual catalysis.



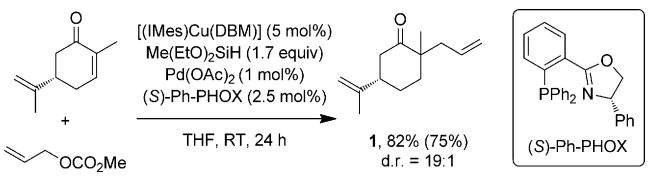
Entry	"Pd complex"		1[a] [%]	d.r.[b]	2[a] [%]	3[a] [%]
1	$[Pd(PPh_3)_4]$ (5 mol%)		29	69/31	0	70
2	$[Pd(PPh_3)_4]$ (1 mol%)		44	69/31	12	17
3	$[Pd_2(dba)_3]$ (0.5 mol%)	dppe (2.5 mol%)	31	73/27	30	21
4	$Pd(OAc)_2$ (1 mol%)	dppe (2.5 mol%)	20	67/33	51	29
5	$Pd(OAc)_2$ (5 mol%)	dppe (12.5 mol%)	0	–	0	33
6	$Pd(OAc)_2$ (2 mol%)	dppe (5 mol%)	9	56/44	47	44
7[c]	$Pd(OAc)_2$ (5 mol%)	dppe (12.5 mol%)	0	–	0	16

[a] Yields determined by ^{1}H NMR spectroscopy. [b] Diastereomeric ratio determined by ^{1}H NMR spectroscopy. [c] 1 mol% of [(IMes)Cu(DBM)] was used.

Optimization of the reaction with regard to the solvent showed that both toluene and THF resulted in complete conversion of the starting material (Table 2, entries 1 and 2). However, the formation of **3** could be almost completely suppressed when THF was used, and it was thus chosen as the optimal solvent. When the reaction was carried out at room temperature, formation of the O-alkylation product (**2**) was favored (80% yield), however, when the reaction was carried out at a higher temperature, the desired C-alkylation product (**1**) became the only alkylated product (79% yield; Table 2, entry 7). In this latter case, no O-alkylation was observed. It should be noted that when the same experiment was stopped after three hours, a mixture of **1**/**2** in a ratio of 38:43 was obtained (Table 2, entry 8), indicating that under these conditions, **2** is formed initially and then transformed into **1** by a Claisen rearrangement, which is probably also catalyzed by palladium.[15a]

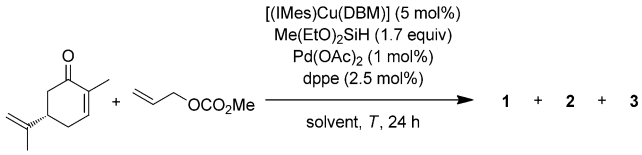
Furthermore, substitution of dppe with (*S*)-Ph-PHOX, a chiral P–N type ligand that is widely used in the Pd^0-catalyzed asymmetric allylic alkylation reaction,[16] increased the diastereoselectivity of **1** up to 90% *de* along with a slight increase in the overall yield (82%; Scheme 3).[15b]

After these satisfying results, we concentrated our efforts on developing an enantioselective version of this reaction, starting with the prochiral substrate **4a** (Scheme 4). Some modifications of the previous conditions were necessary to obtain **5a** with a high yield and high enantioselectivity. In this case, toluene was the better solvent. We also found it crucial to use KO*t*Bu as an additive in order to increase the enantioselectivity.[17] Under these conditions, an interesting side product was observed; the DBM ligand of the copper complex reacted with the π-allyl–Pd species to form the diallylated DBM.[18] To avoid this reaction, [(IMes)Cu(DBM)] was substituted by [(IMes)CuCl]. Final optimization of the phosphine ligand showed that (*S*)-*t*Bu-PHOX significantly increases the enantioselectivity of the reaction, giving **5a** in 83% yield and with 87% *ee*.



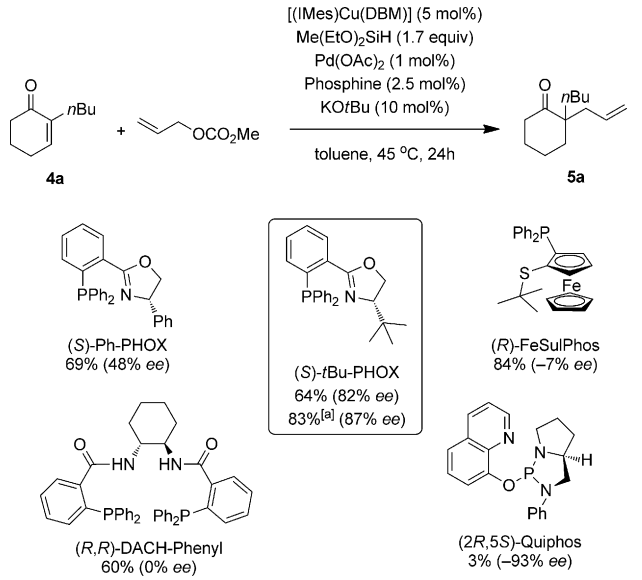
Scheme 3. Optimized conditions for **1**.

Table 2: Variation of the solvent and temperature.



Entry	Solvent	*T* [°C]	**1**[a] [%]	d.r.[b]	**2**[a] [%]	**3**[a] [%]
1	toluene	RT	20	67/33	51	29
2	THF	RT	12	61/39	80	8
3	CH_2Cl_2	RT	trace		–	12
4	CH_3CN	RT	–		–	11
5	THF	0	3	n.d.	6	91
6	THF	10	8	61/39	23	69
7	THF	45	79	67/33	0	21
8[c]	THF	45	38	60/30	43	19

[a] Yields determined by ^{1}H NMR spectroscopy. [b] Diastereomeric ratios determined by ^{1}H NMR spectroscopy. [c] Reaction ran for 3 h. n.d. = not determined.

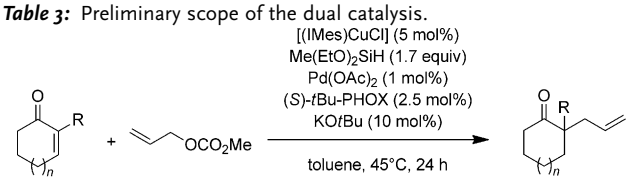


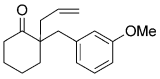
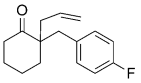
Scheme 4. Effect of the ligand on the enantiomeric excess of **5a**. [a] [(IMes)CuCl] was used instead of [(IMes)Cu(DBM)] and 2.0 equiv of methyl allyl carbonate.

The optimal conditions thus obtained were then applied to other cyclic enones (Table 3). The reaction showed a tolerance toward alkyl and benzyl groups, and the corresponding products were obtained with comparable yields and enantioselectivities (Table 3, entries 1–7). The phenyl group is also tolerated under these conditions, and **5h** was obtained in a good yield, but unfortunately with low enantioselectivity (Table 3, entry 8). Furthermore, Michael acceptors with 6-membered rings (Table 3, entries 1–4, 7 and 8) as well as 5-membered rings (entries 5 and 6) undergo the reaction using our optimized conditions.

The optimization reactions described above gave us valuable information on the mechanism of the reaction. It appears that the two catalytic cycles are intrinsically linked,

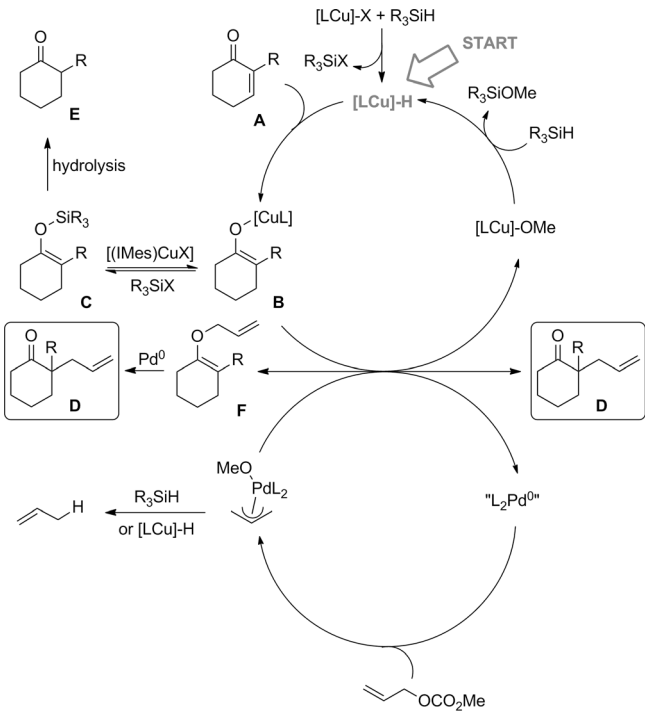
Table 3: Preliminary scope of the dual catalysis.



Entry	Product[a]		Yield[b] [%]	*ee*[c] [%]
1		**5a**	83 (58[d])	87
2		**5b**	79 (63[d])	84
3		**5c**	78	86
4		**5d**	72	72
5		**5e**	40	77
6		**5f**	54	75
7		**5g**	64	43
8		**5h**	75[d]	23

[a] Starting material prepared according to reported procedures (see the Supporting Information). [b] Yields determined by GC analysis and ^{1}H NMR spectroscopy. [c] Determined by GC or HPLC analysis on a chiral stationary phase. [d] Isolated yields.

and that the active species formed in the first cycle reacts with the one formed in the second cycle (Scheme 5). Cu^I hydride, which is preformed in situ, reacts with **A** to form the copper enolate species **B**, which is in equilibrium with the silyl enolate **C**.[10g] At the same time, the Pd^0 complex adds to the methyl allylcarbonate to form the π-allyl–Pd species. Although silyl enolates are well-known nucleophiles for the allylic alkylation reaction,[12m,n] this particular silyl enolate does not react with the π-allyl–Pd moiety, under these conditions, in the absence of the copper catalyst.[19] Hydrolysis of **C** leads to the reduction product **E**. These observations led us to believe that copper enolate **B** is in fact the active species. It reacts with the π-allyl–Pd complex to form the desired product **D** and the O-alkylation product **F** and regenerate the two active metal species. This last step seems to be energy dependent (Table 2), thus giving rise to a possible independent third catalytic cycle at higher temperatures. In this third catalytic cycle, **F** is transformed into **D** through Claisen rearrangement.[15b] A full investigation of the reaction mechanism is still ongoing, and a detailed analysis will be reported in due course.



Scheme 5. Proposed mechanism of the dual catalysis.

Cooperative dual catalysis in domino processes is emerging as an important approach for the development of more time-efficient and less wasteful synthetic pathways.[7] In conclusion, we herein report a Cu/Pd dual catalysis reaction based on the catalytic coupling of the two organometallic intermediates. Thus, the Cu^{I} catalytic cycle generates the starting material for the Pd^{0} catalytic cycle. Although the reagents are present in stoichiometric amounts in the reaction mixture and are in principal able to trap both active species (four different possible pathways), the reaction proceeds as desired.

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Keywords: asymmetric allylic alkylation · copper · dual catalysis · Michael acceptors · palladium

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[17] Investigations into the role of KO*t*Bu are ongoing.

[18] See the Supporting Information (page S-12).

[19] See the Supporting Information (page S-13).

