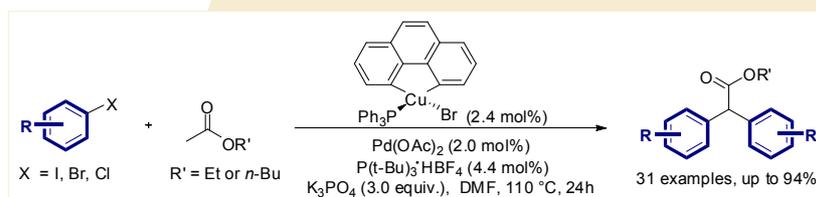


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A bimetallic palladium/copper catalyst system was found to effectively promote the diarylation of alkyl acetates with aryl halides under unprecedentedly mild conditions. The phenanthroline copper phosphine catalyst stabilizes the enolate intermediate to the extent that the deprotonation of esters can be achieved even with the mild base potassium phosphate. The palladium tri-*t*-butylphosphine co-catalyst mediates the coupling of the resulting copper enolate with a wide variety of aryl halides with selective formation of the corresponding diarylacetic acid esters.



Diarylacetic Acid Derivatives

The synthesis of diarylacetic acid derivatives is of considerable interest since many of these structures display unique biological and pharmaceutical activities.^[1]

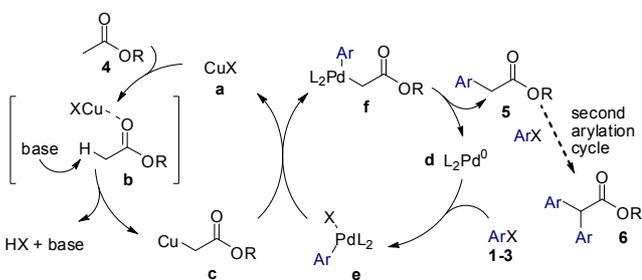


Known syntheses of α -diarylacetate esters include the α -arylation of 2-arylacetates and malonates with hypervalent organoiodine reagents, the arylation of α -aryl- α -diazoacetates with boron reagents, and the α -arylation of 2-arylacetates using palladium- or titanium-catalysts.^[2] However, the preparative utility of these strategies is hampered by the limited availability of the required starting materials.

In this respect, the diarylation of acetic acid esters with aryl halides appeared to be a more attractive approach, as these substrate classes are available in great structural variety at low cost. However, in contrast to 2-arylacetates (2-phenylacetate: $pK_{a(DMSO)} = 22.7$) or alkyl ketones (acetone: $pK_{a(DMSO)} = 26.5$), simple acetic acid esters are much harder to deprotonate (ethyl acetate: $pK_{a(DMSO)} = 29.5$),^[3] so that the use of expensive and hard-to-handle bases such as MHMDS (M = K or Na), LDA, or alkali metal alkoxides seems to be unavoidable in arylation processes of these compounds.

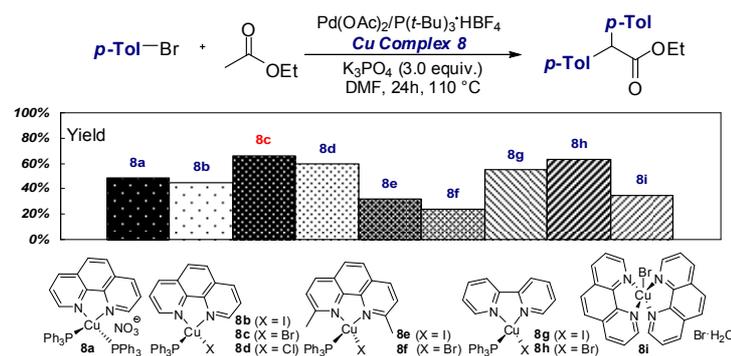
New Strategy for the Synthesis of α -Diarylated Acetates

Our strategy to overcome this key limitation, which significantly hampers the preparative applicability of ester arylations, consisted in employing a co-catalyst that allows the deprotonation of simple acetic acid esters with mild bases by stabilizing the resulting enolates.^[4]

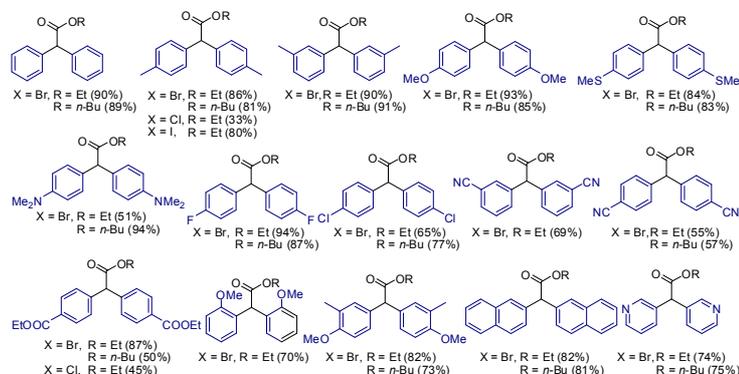


Development of Pd/Cu-Catalyzed Di- α -Arylation of Alkyl Esters

In search for a catalyst system that would allow implementing this reaction concept, we synthesized various copper complexes **8a-l**^[5] and utilized them as co-catalysts in the diarylation of ethyl acetate. The examination of these copper complexes combined with the optimization of other parameters led us to the discovery of a new Pd/Cu-based protocol for the synthesis of diarylacetic acetate.



Under the optimized conditions consisting of 2.0 mol% of Pd(OAc)₂ and 2.4 mol% of [Cu(Phen)(PPh₃)Br] (**8c**), a plethora of electron-rich and electron-deficient aryl- and heteroaryl halides containing various functional groups, e.g. ether, thioether, amine, halide, cyano or ester moieties, were coupled in high yields with alkyl esters. Representative examples of the scope are illustrated below.



Conclusion

The new diarylation method represents a convenient and generally applicable synthesis of alkyl diarylacetates. The discovery that the α -proton of ester could be activated by catalytic amounts of copper species to the extent that it can be removed by a comparably weak base potentially opens up new opportunities for the design of various related coupling reactions with C-H functionalization.

NanoKat
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Literature and Further Reading (see also www.chemie.uni-kl.de/goossen)

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