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Highlights

Cross-Coupling

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Selective Cross-Electrophile Coupling by Dual Catalysis

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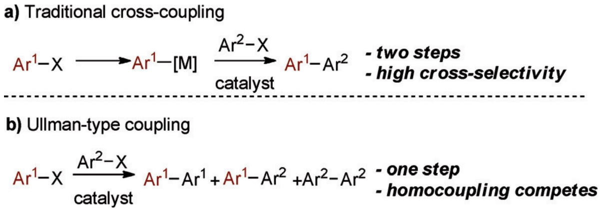
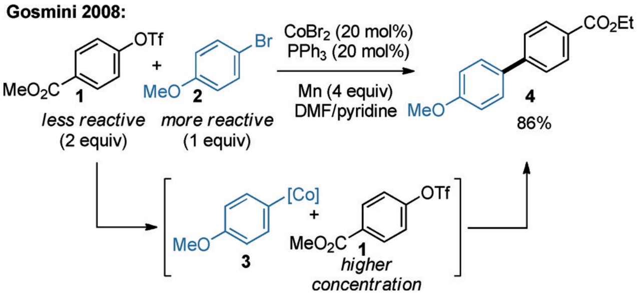
cross-electrophile coupling · dual catalysis · multicatalysis · reductive coupling · Ullman coupling

Chemoselective reactions and their mechanistic aspects have been a fundamental pursuit of methods development. Many reactions have been designed to be inherently selective by employing reaction partners that present dramatically different reactivity profiles. This is true in a traditional cross-coupling reaction: Selectivity is a direct result of one carbon atom being recruited to the metal catalyst through transmetalation and the other by oxidative addition (Scheme 1 a).[1] The selective Ullman-type coupling of two aryl electrophiles has been a particularly interesting challenge, in part because such a reaction would avoid the need to preform an organometallic reagent (Scheme 1 b).[2] However, both electrophiles can compete for oxidative addition with the catalyst, resulting in mixtures of cross-coupling and homocoupling products. Achieving selective cross-coupling instead of homocoupling thus is a significant challenge.[3] Herein, we highlight recent efforts to develop and merge the fields of reductive coupling and multicatalysis to achieve selective cross-electrophile coupling reactions.[4]



Scheme 1. Comparison of selectivity in a) traditional cross-coupling reactions and b) Ullman-type coupling reactions.

To address the challenge of selectivity in cross-electrophile coupling reactions, chemists have typically relied on the use of a single catalyst.[3] When two aryl electrophiles of similar reactivity are employed, a statistical distribution of products is expected. Although there are a wide range of reaction conditions and mechanisms, in general, differences in the relative rates of oxidative addition, the redox potentials, or the steric properties of the competing electrophiles are exploited to minimize homocoupling and maximize the formation of the cross-coupled products (Scheme 2).[3a] Adjusting stoichiometry further improves selectivity; using an excess of the less reactive electrophile will increase the yield of the cross-coupled product and suppress homocoupling of the more reactive electrophile.[3c] However, as the catalyst is inherently more reactive towards one electrophile, homocoupling of that electrophile can be observed as a constant background reaction.



Scheme 2. Representative reductive cross-electrophile coupling reaction. Tf = trifluoromethanesulfonyl.

Breakthroughs in selective oxidative-addition reactions of aryl halides and aryl triflates with palladium catalysts have set the stage for selective dual-catalytic reductive cross-electrophile couplings. Hayashi and Takashi identified palladium catalysts that undergo oxidative addition with aryl triflates in the presence of aryl bromides when an appropriate ligand is added (Scheme 3 a).[5] These results were corroborated by stoichiometric experiments involving the isolation of the corresponding aryl palladium complexes. In related studies, Fu and co-workers demonstrated that ligand effects can have a significant influence on the relative rates of oxidative addition, and even identified catalysts that favor oxidative addition of an aryl chloride over an aryl triflate (Scheme 3 b).[6] In contrast, most nickel complexes undergo oxidative addition more rapidly with aryl bromides than with the corresponding aryl triflates (Scheme 3 c).[3b]

Orthogonal reactivity between catalysts is a key requirement for dual-catalytic reactions to operate smoothly. To design a selective reaction, Weix and co-workers capitalized on the catalysts' orthogonal preferences for oxidative addition (Table 1).[4] By pairing a nickel complex with $PdCl_2$(dppp), they favor cross-reactivity by insuring that each aryl electrophile enters the catalytic cycle by reaction with a different catalyst. In practice, the combination of catalysts provides high cross-selectivity, as well as higher overall reactivity, than either isolated catalyst.

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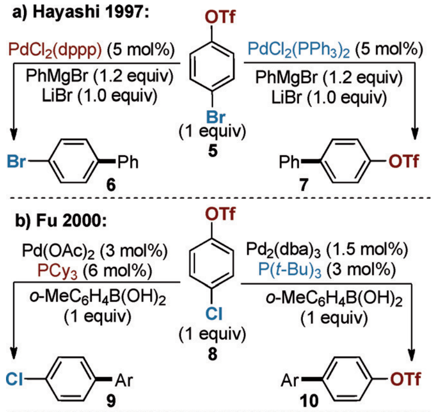
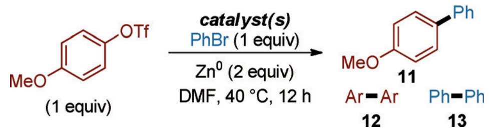


catalyst	ligand	relative rate of oxidative addition
Pd	PPh_3	Br > OTf
Pd	dppp	OTf > Br
Ni	bpy	Br > OTf

Scheme 3. Relative rates of oxidative addition of Group 10 catalysts with aryl halides and triflates. bpy = bipyridine, Cy = cyclohexyl, dba = dibenzylideneacetone, dppp = 1,3-bis(diphenylphosphanyl)propane.

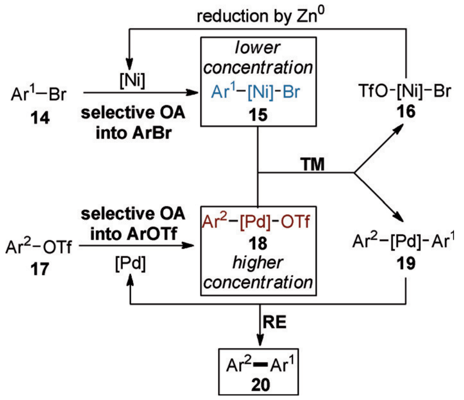
Table 1: Palladium- and nickel-catalyzed Ullman-type coupling reaction.



Entry	Catalyst(s)	**11** [%]	**12** [%]	**13** [%]
1	Pd(dppp)	3	1	4
2	Ni(bpy)	6	6	42
3	Ni(bpy) and Pd(dppp)	67	12	13
4[a]	Ni(bpy) and Pd(dppp)	77	4	7

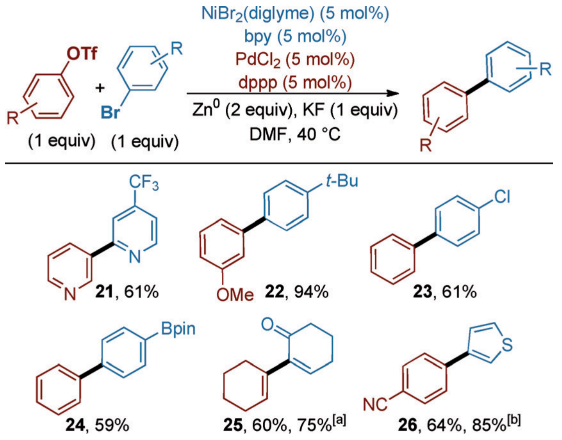
[a] KF (1 equiv) used as an additive.

The proposed mechanism for the reaction contains three key features (Scheme 4). First, the selectivity of each catalyst in oxidative addition regulates the initial selective formation of each aryl metal complex (**15** and **18**). Second, the aryl palladium complex **18** is relatively stable and builds up in the reaction mixture. It does not react with itself, preventing homocoupling of the aryl triflate. Third, aryl nickel intermediate **15**, when formed, is highly reactive and undergoes transmetalation with the first organometallic species that it encounters, typically aryl palladium complex **18**. The relatively low concentration of aryl nickel complex **15** ensures that it does not have the opportunity to react with itself, limiting homocoupling of the aryl bromide. Weix and coworkers drew an analogy between this difference in stability and the relative concentrations of the aryl metal complexes and the "persistent radical effect".[7] This hypothesis was supported by control experiments with only one of the two catalysts (Table 1, entries 1 and 2). Subsequent reductive elimination of diaryl palladium complex **19** regenerates the palladium catalyst; reduction of nickel salt **16** by zinc regenerates the nickel catalyst.



Scheme 4. Proposed mechanism.

Overall, this new approach to the problem of selectivity in reductive cross-electrophile coupling reactions offers a new avenue to access valuable unsymmetric biaryl and diene moieties under mild reaction conditions. An impressive scope was demonstrated with as little as one equivalent of each aryl or vinyl electrophile and with yields as high as 94% (Scheme 5). The reaction is tolerant of a wide range of functional groups, including aryl chlorides, nitriles, and boronic esters. Interestingly, the reaction provides unsymmetric bipyridyl products such as **21** without significant loss in yield or changes in reactivity. Furthermore, diene **25** could be accessed using one equivalent of each electrophile, although higher yields were achieved when two equivalents of 2-bromocyclohexeneone were used.



Scheme 5. Representative scope. [a] Vinyl bromide (2 equiv). [b] Aryl bromide (3 equiv).

For the past three decades, applications of traditional cross-coupling reactions have outpaced those of reductive cross-electrophile coupling reactions. This discrepancy has largely been due to the inadequate homocoupling/cross-coupling selectivities of the latter reaction type. Pairing two catalysts with different reactivity profiles is a new strategy to render Ullman-type reactions chemoselective. This concept will likely see application in related reactions catalyzed by palladium and nickel, including reductive cross-electrophile coupling reactions of a broad range of electrophiles.

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[1] a) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, *Angew. Chem. Int. Ed.* **2012**, *51*, 5062; *Angew. Chem.* **2012**, *124*, 5150; b) E.-I. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340.
[2] J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359.
[3] a) M. Amatore, C. Gosmini, *Angew. Chem. Int. Ed.* **2008**, *47*, 2089; *Angew. Chem.* **2008**, *120*, 2119; b) C. E. I. Knappke, S. Grupe, D. Gartner, M. Corpet, C. Gosmini, A. J. von Wangelin, *Chem. Eur. J.* **2014**, *20*, 6828; c) D. J. Weix, *Acc. Chem. Res.* **2015**, *48*, 1767; d) T. Moragas, A. Correa, R. Martin, *Chem. Eur. J.* **2014**, *20*, 8242.
[4] L. K. G. Ackerman, M. M. Lovell, D. J. Weix, *Nature* **2015**, *524*, 454.
[5] K. Takashi, T. Hayashi, *Tetrahedron Lett.* **1997**, *38*, 7087.
[6] a) A. F. Littke, C. Dai, G. C. Fu, *J. Am. Chem. Soc.* **2000**, *122*, 4020; b) F. Schoenebeck, K. N. Houk, *J. Am. Chem. Soc.* **2010**, *132*, 2496.
[7] A. Studer, *Chem. Eur. J.* **2001**, *7*, 1159.

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