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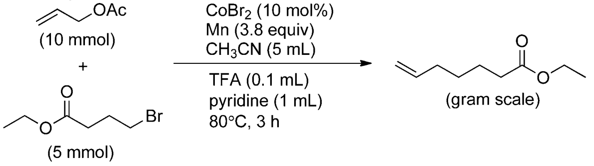
**Cross-Coupling**

# Cobalt-Catalyzed Reductive Allylation of Alkyl Halides with Allylic Acetates or Carbonates

*Xin Qian, Audrey Auffrant, Abdellah Felouat, and Corinne Gosmini**

Transition-metal-catalyzed allylic alkylations, using a broad range of metal complexes, have been intensively studied because of their potential applications in the synthesis of new olefinic compounds in particular for total synthesis.[1] Soft nucleophiles are usually used in Pd-,[1] Mo-,[2] Ir-,[3] Ru-,[4] Rh-,[5] Pt-,[6] and even Fe-catalyzed[7] allylic substitutions. Ni,[8] Co,[9] and Cu[10] catalysts allow the use of hard nucleophiles such as alkylzinc or Grignard reagents, but limited functional group compatibility and/or poor regioselectivity can be observed if the system is not designed carefully. To avoid handling the air- and moisture-sensitive organomagnesium and organozinc reagents, straightforward procedures, which do not require organometallic reagents, are highly desirable and many have now been developed.[11] To the best of our knowledge, direct transition-metal-catalyzed alkyl–allyl cross-couplings using in situ generated catalytic organometallic reagents are still unknown. However, a few years ago, we reported a related Co-catalyzed coupling reaction of aryl halides with allylic acetates;[12] these reactions in the presence of an appropriate reducing reagent, gave allylaromatic compounds. Such allylic carboxylates, whilst less reactive than allyl halides, are much more environmentally friendly.

**Table 1:** Optimized Reaction Conditions.



| Entry | Deviation from Standard Conditions | Yield [%][a] |
|---|---|---|
| 1 | None | 90 |
| 2 | CoBr$_2$ (5 mol%) | 43 (91)[b] |
| 3 | CoBr$_2$ (20 mol%) | 77 |
| 4 | Co(acac)$_2$ (10 mol%) | – |
| 5 | Mn (1.9 equiv) | 17[a] |
| 6 | Zn (3.8 equiv) instead of Mn | – |
| 7 | DMF instead of CH$_3$CN | trace |
| 8 | Allyl acetate (1 equiv) | 47 (67)[c] |
| 9 | No pyridine | 27 |
| 10 | pyridine (2 mL) | 67 |
| 11 | Bipyridine instead of pyridine | 18[b] |
| 12 | PPh$_3$ instead of pyridine | trace[b] |
| 13 | No TFA | – |
| 14 | 35 °C | trace |
| 15 | 50 °C | 43[a] |

[a] Yields were calculated by GC analysis using dodecane as an internal standard. [b] The reaction time is 16 h. After 16 h, there may be still some starting material. [c] Used 1.1 equiv of allyl acetate. acac = acetoacetonate, DMF = *N*,*N'*-dimethylformamide, TFA = trifluoroacetic acid

Given our previous experience with the direct Co-catalyzed functionalization, including alkylation,[11c] of aryl halides[13] we were interested to take the chemistry further, and herein we report a new and general method for direct reductive cross-coupling of allylic acetates with alkyl halides using a CoBr$_2$/Mn system with an acetonitrile/pyridine solvent mixture. The approach accommodates a variety of simple and functionalized alkyl halides and substituted allylic compounds and is experimentally straightforward. Indeed it uses off-the-shelf reagents without any particular precautions against air and moisture. First, we investigated the use of the readily available yet poorly reactive ethyl 4-bromobutanoate with a simple allyl acetate as the electrophile. The major challenge here lies in promoting cross-coupling rather than the formation of reduction and homocoupling products. A combination of factors enabled us to overcome these difficulties (Table 1). The reaction conditions we established as standard afforded an excellent yield within 3 hours (Table 1, entry 1). A 5 mol% catalyst loading gave the same result but over a period of 16 hours, (Table 1, entry 2) and a 20 mol% CoBr$_2$ loading accelerated the reaction (2 hours) but gave a higher quantity of the alkyl dimer according to GC analysis (Table 1, entry 3). Co(acac)$_2$ showed no catalytic activity (Table 1, entry 4). Reducing the amount of Mn dust decreased the reaction rate and the yield (Table 1, entry 5), while replacing Mn by Zn dust resulted in no formation of cross-coupling product (Table 1, entry 6). Equally, no cross-coupling product was detected upon changing CH$_3$CN for DMF (Table 1, entry 7). An excess of the allyl acetate was required to drive the reaction to completion because of the formation of a π-allyl Co complex (Table 1, entry 8); the pyridine appears to be important in stabilizing the low-valent Co intermediate because cross-coupling yields decreased in its absence (Table 1, entry 9). Replacing pyridine by bipyridine or triphenylphosphine gave poor yields, with more than 50% alkyl halide remaining unconsumed (Table 1, entries 11 and 12). The Co/Mn system requires activation by trifluoroacetic acid (TFA) for the formation of the low-valent Co intermediate, and attempts to run the reaction in the absence of this activator gave no cross-coupling product (Table 1, entry 13). At 35 °C, almost no reaction occurred (Table 1, entry 14) and conversion remained low at 50 °C, with the alkyl halide being only partially consumed even after 16 h (Table 1, entry 15).

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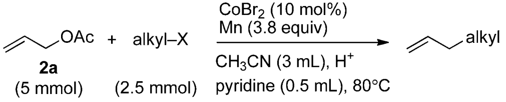
Other substrates were tested in place of allylic acetate, including allyl alcohol, alkyl acetates (benzyl acetate included), aryl acetates/carbonates, and prop-2-yn-1-yl acetate. Unfortunately, no reaction was observed in any of these cases.

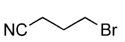
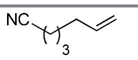
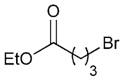
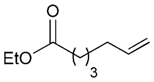
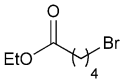
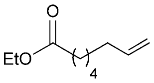
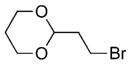
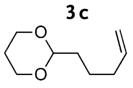
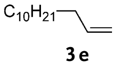
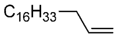
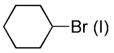
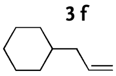
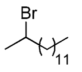
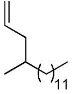
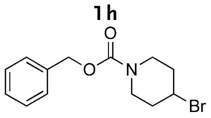
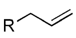
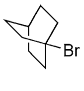
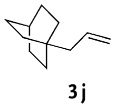
With these results in hand, we first screened various alkyl halides with allyl acetate. The results reported in Table 2 and Table 3 demonstrate that the reaction has a good functional-group tolerance. Functional groups such as nitriles, esters, a dioxane, a carbamate, and chlorine are nicely tolerated (Table 2 and Table 3)[14] and the reaction also proceeded well with long-chain alkyl halides (Table 2, entries 5 and 6). The coupling of secondary alkyl bromides (either cyclic or acyclic) was achieved in high yield (Table 2, entries 7–9) and even the tertiary alkyl bromide **1j** afforded the product **3j** in moderate quantities (Table 2, entry 10). Generally, the reaction reaches completion within 4–6 h, although coupling with tertiary alkyl halides required longer reaction times. The results are therefore in general accord with the suggestion by Oshima[9c] that cobalt catalysts are superior to Ni[15] and Cu[16] for the coupling of two quaternary carbon centers.

Next we investigated the scope of allyl acetates (Table 3). *trans*-Crotyl acetate (**2b**) coupled with primary and secondary alkyl halides in good albeit slightly lower yields than those obtained with unsubstituted allyl acetate (Table 3, entries 1–3).

The formation of the isomeric α and γ products from substituted allyl acetate in allyl–alkyl cross-coupling reactions is known to occur in the Cu-catalyzed system[10] and both

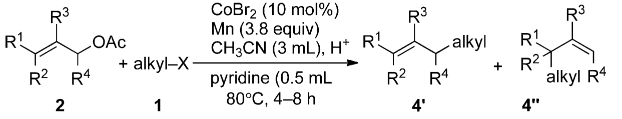
***Table 2:*** Scope of alkyl halides.

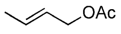
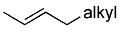
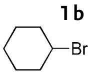
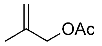
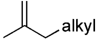
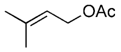
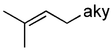
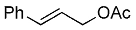
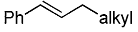
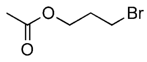
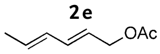
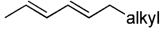
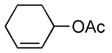
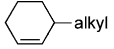
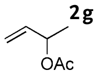
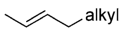
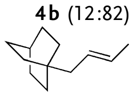
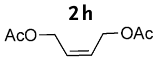
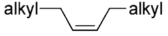


| Entry | Alkyl-X | Product **3** | Yield [%][a] |
|---|---|---|---|
| 1 |  **1a** |  **3a** | 90 |
| 2 |  **1b** |  **3b** | 88 |
| 3 |  **1c** |  **3c** | 90 |
| 4 |  **1d** |  **3d** | 70 |
| 5 | $C_{10}H_{21}Br$ **1e** |  **3e** | 75[b,c] |
| 6 | $C_{16}H_{33}Br$ **1f** |  **3f** | 71[b,c] |
| 7 |  **1g** |  **3g** | 81[a] (85)[d] |
| 8 |  **1h** |  **3h** | 85[b] |
| 9 |  **1i** |  **3i** | 70[c,e,f] |
| 10 |  **1j** |  **3j** | 60[b,c,e] |

[a] Yield of the isolated product. [b] The yields were determined by corrected GC using dodecane as an internal standard. [c] The reaction time was 10 h. [d] Yield from the cyclohexyliodide, as calculated using GC. [e] Mixture of alkyl–H and alkyl–alkyl. [f] The yields were determined by $^1$H NMR spectroscopy.

***Table 3:*** Scope of allylic acetates.



| Entry | Allylic acetate | Alkyl-X | Product **4** (Ratio 4′/4′′) | Yield [%][a] |
|---|---|---|---|---|
| |  | |  | |
| 1 | **2b** | **1a** | **4a** (85:15) | 63 |
| 2 | **2b** | **1b** | **4b** (89:11) | 72 |
| | |  | | |
| 3 | **2b** | **1g** | **4c** (95:5) | 75[b] |
| |  | |  | |
| 4 | **2c** | **1b** | **4d** | 88[b] |
| |  | |  | |
| 5 | **2d** | **1b** | **4e** (78:22) | 67 |
| |  | |  | |
| 6 | **2e** | **1a** | **4f** (>99:1) | 71 |
| 7 | **2e** | **1b** | **4g** (>99:1) | 81 |
| | | $Cl(CH_2)_4Br$ | | |
| 8 | **2e** | **1j** | **4h** (>99:1) | 77 |
| | | $CN(CH_2)_2Cl$ | | |
| 9 | **2e** | **1k** | **4i** (>99:1) | 98 |
| | |  | | |
| 10 | **2e** | **1l** | **4j** (>99:1) | 68 |
| |  | |  | |
| 11 | **2f** | **1b** | **4k** (92:8)[c] | 52 |
| |  | |  | |
| 12 | **2g** | **1b** | **4l** | 38 |
| |  | |  | |
| 13 | **2h** | **1b** | **4b** (12:82) | 56 |
| | | |  | |
| 14 | **2h** | **1j** | **4m** (15:85) | 66 |
| |  | |  | |
| 15 | **2i** | **1a** | **4n**[d] | 76 |

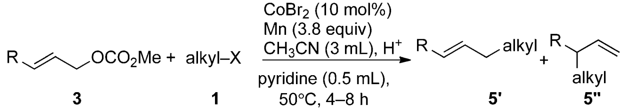
[a] Yield of isolated 4 and 4′. [b] The yield was determined by $^1$H NMR spectroscopy. [c] In this case the minor product comes from an attack at the methyl-substituted carbon atom (ε position). [d] Mixture of bis and mono γ-alkylated products bearing an acetate group in a 81:19 ratio.

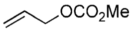
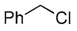
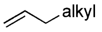
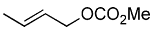
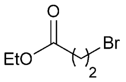
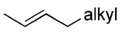
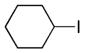
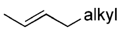
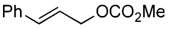
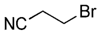
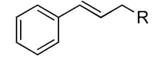
products were detected in our reactions. However, the linear product **4′** always dominated (with a minimal proportion of 78%; Table 3, entry 5). The **4′**/**4″** ratio was determined by $^{1}$H NMR spectroscopy. But-3-en-2-yl acetate (**2c**) reacted with the primary alkyl halide **1b** (Table 3, entry 4) but not the secondary alkyl halide **1g**. More sterically hindered acetates, such as prenyl acetate (**2d**), reacted with **1b** and provided the cross-coupling product in a good yield (Table 3, entry 5), but again no coupling product was observed with secondary alkyl bromide **1g**. Excellent yields were obtained using (*E*)-cinnamyl acetate (**2e**; Table 3, entries 6–9). The alkylation reaction of 1-bromo-4-chlorobutane resulted in a selective attack at the bromide site, thus affording (*E*)-7-chlorohept-1-en-1-ylbenzene (**4h**) in good yield (Table 3, entry 8). Interestingly, when a chloro group was present β to the nitrile, an excellent yield of the cross-coupled product **4i** was obtained (Table 3, entry 9). Having observed that no cross-coupling occurs with bromoalcohols, we employed the acylated alcohol **1l** with success (Table 3, entry 10). Importantly, no branched coupling product could be detected with the phenyl-substituted allylic acetate **2e**. The conjugated allylic acetate **2f** could also be used, although the yields were lower than those obtained from allyl or cinnamyl acetates (Table 3, entry 11). Next we investigated the reactivity of secondary allylic acetates. The cyclohex-2-en-1-yl acetate (**2g**) reacted with **1b** to give the product in poor yield; the high reactivity of the primary alkyl halide leads to the formation of by-products (Table 3, entry 12). The acyclic secondary allylic acetate **2h** reacted with both primary and tertiary alkyl halides to give mainly the linear coupling product in moderate yield (Table 3, entries 13 and 14). Unsurprisingly, double alkylation of *cis*-1,4-diacetoxy-2-butene with **1a** was the main reaction observed; the reaction proceeded with retention of stereochemistry to give the *Z* product in good yield (Table 3, entry 15).

During the screening of alkyl halides, we found that both the presence of electron-withdrawing substituents, such as nitrile or ester groups, in the β position relative to the reactive bromo functionality and the use of benzyl chloride prevented the coupling reaction. This prompted us to employ the more reactive series of allyl carbonates. After minor modifications to the standard protocol allyl carbonates, including crotyl carbonate and cinnamyl carbonate, were successfully coupled to such halides (Table 4). In the case of *trans*-crotyl carbonate, the reaction with a primary alkyl halide gave primarily the terminal coupling product (Table 4, entry 2). Note that with bulkier cinnamyl carbonates, only the linear product was detected (Table 4, entry 4). The reaction also worked efficiently with the secondary alkyl halide, cyclohexyl iodide (Table 4, entry 3). However, the more-reactive α-substituted alkyl halides, such as ethyl 2-chloro/bromo acetate, could not be coupled with allylic carbonates. To our best of our knowledge, very few reports deal with C–C coupling of these reactive alkyl halides.[17]

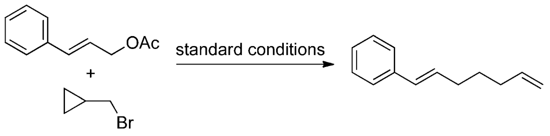
A few experiments were conducted to provide some insight into the mechanism of this allyl–alkyl cross coupling reaction. When bromomethylcyclopropane was reacted with (*E*)-cinnamyl acetate, the ring-opened product (*E*)-hepta-1,6-dien-1-ylbenzene was detected by GC as the sole cross-coupling product [Eq. (1)]. Moreover, the addition of the free radical 2,2,6,6-tetramethylpiperine-1-oxyl (TEMPO) before the alkyl halides inhibited the cross-coupling reaction. These results point towards the involvment of an alkyl radical intermediate in the activation process of the alkyl halide .

***Table 4:*** Scope of allylic carbonates and alkyl halides.



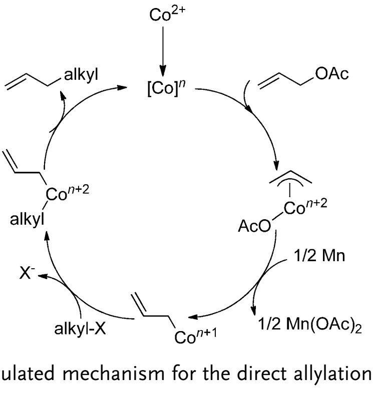
| Entry | Allylic carbonate | Alkyl-X | Product (5′/5″) | Yield [%] |
|---|---|---|---|---|
| 1 |  **3a** |  **1l** |  **5a** | 95[a] |
| 2 |  **3b** |  **1m** |  **5b** (87:13)[c] | 82[b] |
| 3 | **3b** |  **1g** |  **4c**[c] (89:11) | 70[a] |
| 4 |  **3d** |  **1n** |  **4i** (>99:1)[c] | 93[b] |

[a] Yield determined by GC using dodecane as an internal standard. [b] Combined yield of isolated **5′** and **5″**. [c] Ratio of linear/branched.



(1)

Our current mechanistic hypothesis is presented in Scheme 1. Initial reduction of the Co$^{II}$ precatalyst should furnish a catalytically active low-valent Co species. Subsequent oxidative addition to the allyl acetate forms an allyl Co intermediate that is again subjected to reduction by manganese dust. This allyl Co complex reacts with an alkyl halide to give an allyl alkyl Co complex through the formation of an alkyl radical. Then reductive elimination occurs to furnish the cross-coupling product along with the regeneration of the active species.



***Scheme 1.*** Postulated mechanism for the direct allylation of alkyl halides.

In summary, a new route for the direct allylation of various alkyl halides catalyzed by simple cobalt(II) bromide was developed. This method is very straightforward, and environmentally friendly. It is efficient for the coupling of a large variety of alkyl halides (primary, secondary, and tertiary) with substituted allylic acetates and carbonates and provides good to excellent yields with good functional group tolerance. Moreover, in the case of substituted allyl acetates, the reaction affords the linear product as the major or the sole product. Both sterically hindered secondary allyl acetates and secondary and tertiary alkyl halides are acceptable as substrates. Further studies to extend the scope of this method and to gain detailed insight into its mechanism are currently underway in our laboratory.

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