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Copper-Catalyzed Nondecarboxylative Cross Coupling of Alkenyltrifluoroborate Salts with Carboxylic Acids or Carboxylates: Synthesis of Enol Esters

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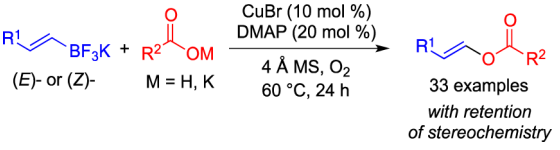
ABSTRACT



A mild copper-catalyzed Chan–Lam–Evans type cross-coupling reaction for the regioselective and stereospecific preparation of (*E*)- or (*Z*)-enol esters is described. The method couples carboxylate salts or carboxylic acids with potassium alkenyltrifluoroborate salts in the presence of catalytic CuBr and DMAP with 4 Å molecular sieves under O_2 at 60 °C. Overall, this method demonstrates carboxylic acids as suitable reaction partners for nondecarboxylative copper-catalyzed cross-couplings to form C–O bonds in an Ullmann-like reaction.

Transition metal catalyzed cross-couplings to form C–O, C–N, and C–S bonds have emerged as powerful methods in organic synthesis. The formation of C–O bonds, for example, can be accomplished by Pd-based cross-coupling of halides,[1] or through Cu-based cross-coupling of organometalloids under oxidative conditions (Figure 1a).[2] While such methods employing alcohols or phenols as cross-coupling partners are routinely used, the use of other oxygen-based nucleophiles is unusual. In particular carboxylic acids constitute a general class of oxygen-based nucleophile that is rarely encountered for metal-catalyzed C–O bond formation. Instead, carboxylic acids[3] are primarily utilized as nucleophilic cross-coupling partners for C–C bond formation under decarboxylative conditions (Figure 1b),[4–7] and as *ortho*- directing groups for C–H functionalizations.[8,9] Isolated examples of C–O bond formation from carboxylic acids using alkenyl or aryl halides,[10] or with organometalloid derivatives,[11,12] often suffer from problems such as low yields, the use of stoichiometric metals, high catalyst or reagent loadings, and high reaction temperatures (Figure 1c). During the

(1) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., Ed.; J. Wiley & Sons Inc.: New York, 2002; pp 1097–1106.

(2) Copper-mediated cross-coupling reactions are a powerful tool for C–O, C–N and C–S bond formation, see: (a) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed. Engl.* **2009**, *48*, 6954–6971. (b) Dehli, J. R.; Legros, J.; Bolm, C. *Chem. Commun.* **2005**, 973–986. (c) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337–2364. (d) Nelson, T. D.; Crouch, R. D. *Org. React.* **2004**, *63*, 265–555. (e) Thomas, A. W.; Ley, S. V. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449. (f) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469.

(3) For a review on the use of carboxylic acids in catalysis, see: Gooßen, L. J.; Rodríguez, N.; Gooßen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100–3120.

(4) See for example: (a) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250–11251. (b) Forgione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350–11351. (c) Gooßen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662–664. (d) Gooßen, L. J.; Rodríguez, N.; Linder, C. *J. Am. Chem. Soc.* **2008**, *130*, 15248–15249. (e) Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194–4195. (f) Gooßen, L. J.; Rodriguez, N.; Lange, P.; Linder, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 1111–1114. (g) Zhang, F.; Greaney, M. F. *Angew. Chem., Int. Ed.* **2010**, *49*, 2768–2771. (h) Lindh, J.; Sjoberg, P. J. R.; Larhed, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 7733–7737. (i) Shang, R.; Ji, D.-S.; Chu, L.; Fu, Y.; Liu, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 4470–4474. (j) Rodriguez, N.; Gooßen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030–5048.

(5) One reason that couplings of carboxylic acids have not been extensively studied is that the conditions and temperatures typically required for C–O bond formation using cross-coupling methods, as for example in Buchwald–Hartwig chemistry, could lead to competing decarboxylation or protonation.

(6) For recent examples of C–N bond formation via copper-catalyzed decarboxylative cross-coupling of carboxylic acids, see: (a) Jia, W.; Jiao, N. *Org. Lett.* **2010**, *12*, 2000–2003. (b) Zhang, Y.; Patel, S.; Mainolfi, N. *Chem. Sci.* **2012**, *3*, 3196–3199.

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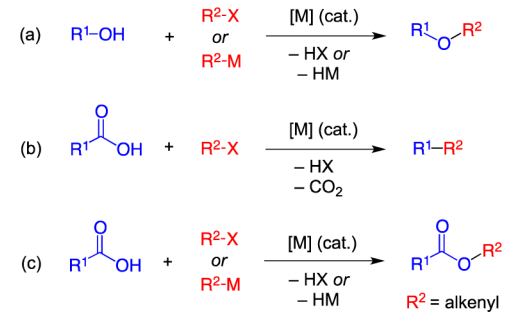


Figure 1. Cross-coupling reactions leading to C–O or C–C bond formation.

course of our studies, Cheng has reported the reaction of aryl carboxylic acids with arylboronic acids,[13] and Liu and co-workers demonstrated the use of a mixed copper/silver promoted arylation of aryl carboxylic acids with arylboronic acids.[14] This reaction required the use of $Cu(OTf)_2$ (20 mol %) and Ag_2CO_3 (2 equiv) at 120 °C and was also applied to three examples using styrylboronic acid. We now report the development of a stereospecific catalytic copper(II)-based cross-coupling method for the *nondecarboxylative* cross-coupling of carboxylic acids with alkenylboron derivatives to give enol esters under mild conditions that does not require the use of stoichiometric metal additives (Figure 1c).

Enol derivatives such as enol esters serve as key synthetic building blocks in organic, medicinal, and polymer chemistry, and are found in many target molecules including many diverse natural products.[15] The classical approach to enol ester synthesis involves enol or enolate trapping. More recent approaches to their synthesis include metal catalyzed (e.g., Ru, Ir, and Re) additions of carboxylic acids to alkynes,[16] isomerizations of allylic esters,[17] and carbonylative arylations of aryl ketones.[18] Control of enol ester regiochemistry (i.e., Markovnikov versus anti-Markovnikov products) and *E*/*Z* diastereoselectivity can be an issue with such reactions. We envisaged that the use of a carboxylic acid-based cross-coupling strategy could potentially provide a solution to these issues, using stereodefined potassium alkenyltrifluoroborate salts. Organoboron compounds serve as valuable cross-coupling partners for C–O/N/S bond formation.[19,20] Chan and Evans originally reported the use of boronic acids as cross-coupling partners with phenols under copper-catalyzed conditions to form C–O bonds.[21] Potassium organotrifluoroborate salts[22] were subsequently revealed to be suitable partners for copper-catalyzed cross-couplings with phenols and aliphatic alcohols,[23,24] as well as with amines and amides.[25] Potassium alkenyltrifluoroborate salts are readily formed from the corresponding boronic acids with KHF_2,[26] but are more stable and readily handled.

Initial reaction optimization for the coupling of potassium (*E*)-trifluorohexenylborate with a variety of

(7) For an example of C–O bond formation via copper-catalyzed decarboxylative cross-coupling of carboxylic acids, see: Bhadra, S.; Dzik, W. I.; Goossen, L. J. *J. Am. Chem. Soc.* **2012**, *134*, 9938–9941.

(8) See for example: (a) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D. H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.–Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510–3511. (b) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407–1410. (c) Chiong, H. A.; Pham, Q.–N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879–9884.

(9) Cornella, J.; Righi, M.; Larrosa, I. *Angew. Chem., Int. Ed.* **2011**, *50*, 9429–9432.

(10) The direct synthesis of aryl and enol esters from copper-mediated coupling of aryl and vinyl halides with copper carboxylates only occurs at high reaction temperatures under stoichiometric conditions, see: (a) Lefler, S. R.; Rose, S. D. *Synth. Commun.* **1999**, *29*, 3805–3810. (b) Kurata, Y.; Yamamoto, T. *Can. J. Chem.* **1983**, *61*, 86–91. (c) Klumpp, G. W.; Schakel, B. M.; Schmitz, R. F.; Vrielink, J. J. *Tetrahedron Lett.* **1975**, *16*, 3429–3432. (d) Commercon, A.; Normant, J.; Villieras *J. Organomet. Chem.* **1975**, *93*, 415–421. (e) Cohen, T.; Wood, J.; Dietz, A. G., Jr. *Tetrahedron Lett.* **1974**, *15*, 3555–3558. (f) Cohen, T.; Lewin, A. H. *J. Am. Chem. Soc.* **1966**, *88* (4521), 4522.

(11) (a) Small amounts of aryl acetates form as byproducts in the copper-mediated dimerization of boronic acids, see: Demir, A. S.; Reis, Ö.; Emrullahoglu, M. *J. Org. Chem.* **2003**, *68*, 10130–10134. (b) Small amounts of enol acetates form as byproducts in the Cu(II) promoted reaction of alkenylpentafluorosilicates, see: Tamao, K.; Kakui, T.; Kumada, M. *Tetrahedron Lett.* **1980**, *21*, 4105–4108. (c) For an esterification reaction using an aldehyde and an arylboronic acid, see: Meng, J. J.; Gao, M.; Wei, Y.–P.; Zhang, W.–Q. *Chem. Asian J.* **2012**, *7*, 872–875.

(12) Luo, F.; Pan, C.; Qian, P.; Cheng, J. *Synthesis* **2010**, 2005–2010.

(13) Zhang, L.; Zhang, G.; Zhang, M.; Cheng, J. *J. Org. Chem.* **2010**, *75*, 7472–7424.

(14) Dai, J.-J.; Liu, J.-H.; Luo, D.-F.; Liu, L. *Chem. Commun.* **2011**, *47*, 677–679.

(15) See for example: (a) Wang, G.-C.; Li, T.; Deng, F.-Y.; Li, Y.-L.; Ye, W.-C. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1379–1382. (b) Dai, J.; Sorribas, A.; Yoshida, W. Y.; Williams, P. G. *Phytochemistry* **2010**, *71*, 2168–2173. (c) Fukuyama, Y.; Kubo, M.; Esumi, T.; Harada, K.; Hioki, H. *Heterocycles* **2010**, *81*, 1571–1602. (d) Iliopoulou, D.; Vagias, C.; Harvala, C.; Roussis, V. *Nat. Prod. Lett.* **2000**, *14*, 373–378. (e) Sitachitta, N.; Gerwick, W. H. *J. Nat. Prod.* **1998**, *61*, 681–684. (f) Gavagnin, M.; Mollo, E.; Castelluccio, F.; Montanaro, D.; Ortea, J.; Cimino, G. *Nat. Prod. Lett.* **1997**, *10*, 151–156. (g) Aldrich, J. R.; Avery, J. W.; Lee, C.-J.; Graf, J. C.; Harrison, D. J.; Bin, F. *J. Entomological Sci.* **1996**, *31*, 172–182. (h) Paul, V. J.; Fenical, W. *Phytochemistry* **1985**, *24*, 2239–2243.

(16) See for example: (a) Rotem, M.; Shvo, Y. *Organometallics* **1983**, *2*, 1689–1691. (b) Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *J. Org. Chem.* **1987**, *52*, 2230–2239. (c) Gooßen, L. J.; Paetzold, J.; Koley, D. *Chem. Commun.* **2003**, 706–707. (d) Bruneau, C.; Dixneuf, P. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 2176–2203.

(17) Mamone, P.; Grünberg, M. F.; Fromm, A.; Khan, B. A.; Gooßen, L. J. *Org. Lett.* **2012**, *14*, 3716–3719.

(18) Schranck, J.; Tlili, A.; Neumann, H.; Alsabeh, P. G.; Stradiotto, M.; Beller, M. *Chem.—Eur. J.* **2012**, *18*, 15592–15597.

(19) (a) Chan, D. M. T.; Lam, P. Y. S. In *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2005; pp 205–240. (b) Qiao, J. X.; Lam, P. Y. S. In *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials (Vol. 1 and 2)*, 2nd ed.; Hall, D. G., Ed.; Wiley-VCH: Weinheim, Germany, 2011; pp 315–361. (c) Qiao, J. X.; Lam, P. Y. S. *Synthesis* **2011**, 829–856.

(20) Partyka, D. V. *Chem. Rev.* **2011**, *111*, 1529–1595.

(21) (a) Chan, D. M. T.; Monaco, K. L.; Wang, R. P. *Tetrahedron Lett.* **1998**, *39*, 2933–2936. (b) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937–2940.

(22) For leading references, see: (a) Molander, G. A.; Jean-Gérard, L. *Org. React.* **2013**, *79*, 1–316. (b) Darses, S.; Genet, J. P. *Chem. Rev.* **2008**, *108*, 288–325. (c) Stefani, H. A.; Cella, R.; Vieira, A. S. *Tetrahedron* **2007**, *63*, 3623–3658. (d) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275–286.

(23) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 1381–1384.

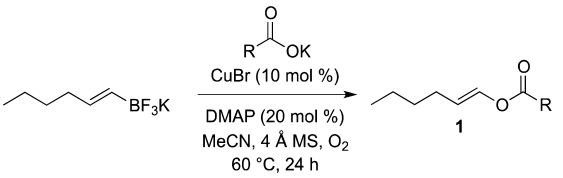
(24) For a mechanistic study on Cu catalyzed C–O bond formation from arylboronic acids, see: King, A. E.; Brunold, T. C.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 5044–5045.

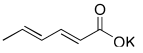
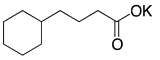
(25) (a) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 4397–4400. (b) Bolshan, Y.; Batey, R. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2109–2112. (c) Bolshan, Y.; Batey, R. A. *Tetrahedron* **2010**, *66*, 5283–5294.

(26) For the use of KHF_2 for organotrifluoroborate formation, see: Vedejs, E.; Fields, S. C.; Shrimpf, M. R. *J. Am. Chem. Soc.* **1993**, *117*, 11612–11613.

potassium carboxylate salts afforded enol esters **1** in excellent yields exclusively as the *trans* isomers (≥98:2 by NMR) (Table 1). Reaction optimization revealed that solvent choice plays a crucial role in the success of the reaction,[27] with polar solvents such as MeCN giving highest yields. The use of DMAP was found to be critical for the success of the reaction, since reaction in the absence of a ligand or the use of other ligands such as TMEDA, 1,10-phenanthroline, pyridine, imidazole, triethylamine, or Hünig's base resulted in only trace amounts of product being observed.

Table 1. Copper-Catalyzed Cross-Coupling of Potassium Carboxylates with Potassium (*E*)-Trifluorohexenylborate[a]



entry	carboxylic acid	product	yield[b]
1	PhCOOK	**1a**	quant
2		**1b**	90%
3	MeCOOK	**1c**	89%
4		**1d**	96%

[a] Reaction conditions: RCOOK (1.0 equiv), $C_6H_{11}BF_3K$ (2.0 equiv). [b] Isolated yields after column chromatography.

While encouraged by the successful cross-coupling of carboxylate salts, a more direct protocol utilizing carboxylic acids would be operationally more convenient, since it would obviate the need for the prior formation of the carboxylate salts. An excellent yield of **1a** was obtained in the coupling of benzoic acid under identical conditions to those employed using carboxylate salts (Table 2, entry 1). Addition of external bases to the reaction led to decreased product yields. Other carboxylic acids could also be used in the reaction under identical reaction conditions using MeCN as the reaction solvent in generally good to excellent yields (Table 2, Protocol A). In the case of sterically hindered aromatic carboxylic acids, the products **1k**, **1l**, and **1m** were isolated in moderate yields. 4-Hydroxybenzoic acid underwent coupling to give not only the desired enol ester **1n**, but also a byproduct resulting from cross-coupling of both the carboxylic acid oxygen and phenolic hydroxyl group. The product distribution obtained in this case is noteworthy, since although phenols have previously been used in cross-couplings with organoboron compounds,[21,23] it suggests that the carboxylic acid functional group is more reactive toward cross-coupling under the current reaction conditions. In some cases, yields of **1** were poor. Further optimization studies revealed that increased reaction temperature or the presence of additional bases did not improve reactivity. However, the use of a MeCN/DMSO (4:1) solvent mixture (Table 2, Protocol B), led to dramatically improved yields, perhaps due to the increased solubility of the reagents under these conditions. Protocol A could also be applied with other potassium (*E*)-alkenylborate salts, yielding (*E*)-enol esters **2** in good yields and diastereoselectivities (≥98:2 by NMR) (Figure 2).

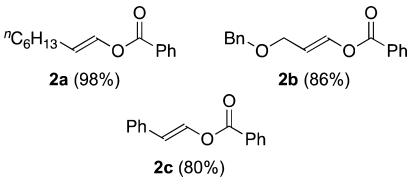


Figure 2. Formation of other enol acetates **2** from potassium (*E*)-alkenylborate salts using Protocol A.

The enol esters **1** and **2** obtained from the cross-coupling reactions of carboxylic acids were obtained as the *trans* isomers (≥98:2 by NMR). Of particular interest from a mechanistic standpoint is whether the coupling reaction is stereospecific. To establish the stereoselectivity of the reaction, potassium (*Z*)-trifluoropropenylborate was used as a coupling partner (*cis*/*trans* ratio = 18:1).[28] Reaction with both electron-rich and electron-deficient benzoic acids or carboxylate salts led to the products **3a**–**d** with high *cis*-selectivity as determined by ^{1}H NMR (Table 3). Since alkene geometry is maintained in the reaction it supports a mechanism involving transmetalation to copper followed by a reductive elimination, similar to those previously proposed in related cross-coupling reactions of organoboron compounds (Figure 3).[19,21,23–25] The stereospecific nature of the coupling is not consistent with reactions involving free-radical intermediates. In addition, there was no evidence for the formation of any products resulting from decarboxylation of the carboxylic acids, as could have occurred, for example, through conversion of intermediate **4** into **5**. The lack of such products presumably reflects the lower temperature employed for the cross coupling than is typically used for decarboxylative cross-couplings.[3–7] Interestingly, the observation of retention of stereochemistry contrasts with Masuda's observations of inversion of stereochemistry in the acetoxylation of alkenylboronic esters by $PhI(OAc)_2$/NaI.[29]

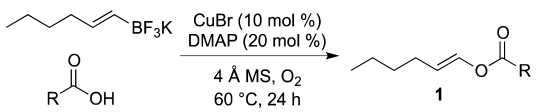
In conclusion, a general stereoselective and regioselective approach to enol ester synthesis has been developed using a copper-catalyzed cross-coupling of alkenyltrifluoroborate salts with carboxylate salts or carboxylic acids. The reaction occurs in a stereospecific manner, is operationally straightforward and avoids the use of other additives such as Ag(I) salts. The method is complementary to metal-catalyzed additions of carboxylic acids to alkynes, and contrasts with the widespread use of carboxylic acids in decarboxylative

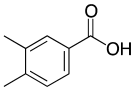
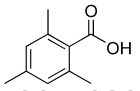
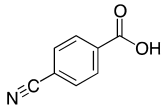
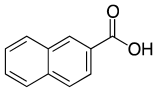
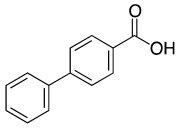
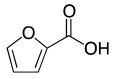
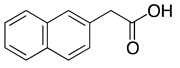
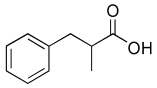
(27) Optimization experiments included the effect of the copper catalyst, ligand, solvent, reaction temperature, and ratio of coupling partners.

(28) Prepared from commercially available (*Z*)-propenylboronic acid.

(29) Murata, M.; Satoh, K.; Watanabe, S.; Masuda, Y. *J. Chem. Soc., Perkin Trans. I* **1998**, 1465–1466.

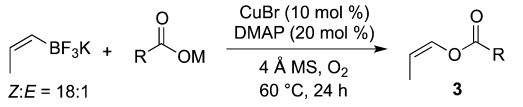
Table 2. Copper-Catalyzed Cross-Coupling of Carboxylic Acids with Potassium (*E*)-Trifluorohexenylborate Using Protocols A and B[a]

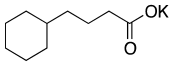
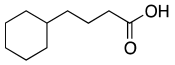
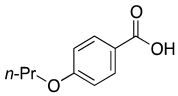
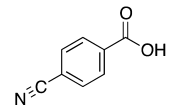


entry	carboxylic acid	product	protocol[a]	yield[b,c]
1	PhCOOH	**1a**	A	93%
2	*p*-TolCOOH	**1e**	A	87%
3	*m*-TolCOOH	**1f**	A	88%
4	4-$MeOC_6H_4COOH$	**1g**	A	91%
5	3-$MeOC_6H_4COOH$	**1h**	A	82%
6	4-$PrOC_6H_4COOH$	**1i**	A	81%
7		**1j**	A	86%
8	*o*-TolCOOH	**1k**	A	62%
9	2-$MeOC_6H_4COOH$	**1l**	A	47%
10		**1m**	A	41%
11	4-HOC_6H_4COOH	**1n**	A	33%
12	4-BrC_6H_4COOH	**1o**	A	78%
13	4-ClC_6H_4COOH	**1p**	A	13%
14	4-ClC_6H_4COOH	**1p**	B	96%
15		**1q**	A	32%
16		**1q**	B	87%
17		**1r**	A	14%
18		**1r**	B	88%
19		**1s**	A	48%
20		**1s**	B	97%
21		**1t**	A	29%
22		**1t**	B	76%
23		**1u**	A	traces
24		**1u**	B	59%
25	$PhCH_2COOH$	**1v**	A	94%
26		**1w**	A	52%
27	$Ph(CH_2)_3COOH$	**1x**	A	90%
28	$Ph(CH_2)_4COOH$	**1y**	A	58%
29	*t*-BuCOOH	**1z**	A	18%

[a] Reaction conditions: RCOOH (1.0 equiv), $C_6H_{11}BF_3K$ (2.0 equiv), using MeCN solvent (Protocol A) or MeCN/DMSO (4:1) solvent (Protocol B). [b] Isolated yields after column chromatography. [c] dr ≥ 98:2 as determined by ^1H NMR analysis.

Table 3. Formation of Enol Acetates **3** from Potassium (*Z*)- Trifluoropropenylborate Using Protocols A and B[a]



entry	precursor (RCOOK or RCOOH)	product	protocol[a]	yield[b,c] (*Z*/*E* ratio)
1	PhCOOK	**3a**	A	88% (41:1)
2		**3b**	A	90% (22:1)
3		**3b**	A	81% (13:1)
4		**3c**	A	71% (21:1)
5		**3d**	B	69% (23:1)

[a] Reaction conditions: RCOOH (1.0 equiv), $C_3H_5BF_3K$ (2.0 equiv), using MeCN solvent (Protocol A) or MeCN/DMSO (4:1) solvent (Protocol B). [b] Isolated yields after column chromatography. [c] dr determined by ^1H NMR analysis.

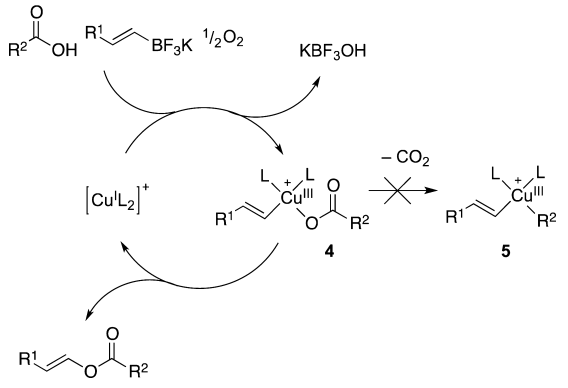


Figure 3. Mechanistic overview of enol acetate formation.

cross-coupling reactions. Further studies on cross-coupling reactions and applications of potassium organotrifluoroborate salts will be reported in due course.

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Supporting Information Available. Full experimental details and characterization data for all compounds including ^1H and ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.