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PPh_3-mediated intramolecular conjugation of alkyl halides with electron-deficient olefins: facile synthesis of chromans and relevant analogues†

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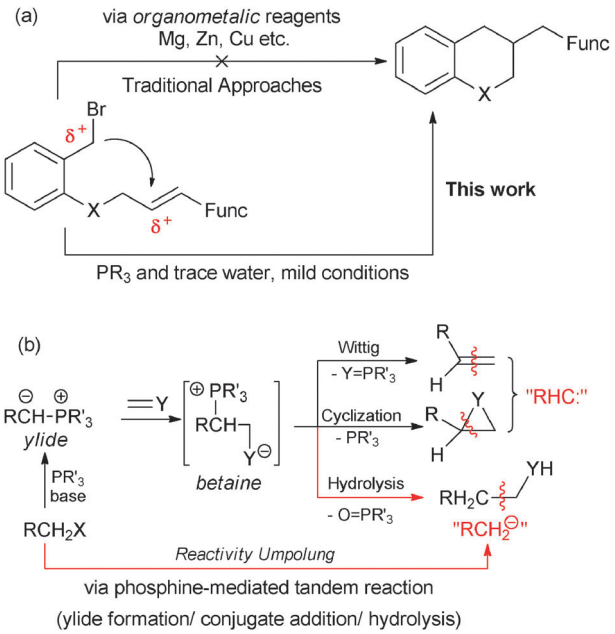
With the mediation of phosphine, the direct intramolecular coupling of two electrophiles – alkyl halides with electron-deficient olefins – has been successfully realized in an intramolecular conjugate addition manner. The reaction provides a new approach for the synthesis of chromans and relevant analogues.

A common strategy for conjugating the alkyl group of simple halides with electron-deficient olefins is by radical cyclization or to convert alkyl halides into the corresponding organometallic reagents such as the Grignard reagents, organolithium or zinc compounds *etc.* and then run a conjugate addition, normally in the presence of a catalytic amount of dry cuprous salts.[1–5] However, this strategy proved to be inefficient for the intramolecular reactions of the substrates shown in Scheme 1a.[4,5] Recently, during the course of our investigation of the ylide-initiated Michael addition cyclization reactions (YIMAC),[6] we discovered a non-metal phosphine-mediated approach to realize this coupling by integrating a hydrolysis step[7] to reduce the betaine intermediates. In this tandem reaction, phosphine mediates a formal reactivity umpolung of the alkyl halides, different from typical phosphorus ylide reactions like the Wittig reaction and small ring formation reactions in which the phosphines are more like a "RHC:" carrier (Scheme 1b).[7g] This new reaction allows a facile conjugation of two electrophilic units in the presence of water, and is compatible with ester solvents and various functionalities like halide, ketone, ester, amide, nitrile, ether *etc.*, in contrast to the harsh reaction conditions required when handling organometallic reagents.[1–3] Importantly, this reaction also provides a novel and facile approach for the syntheses of other chroman analogues such as thiochromans, tetrahydroquinolines, and tetralines, which are useful synthetic intermediates and also of broad biological and pharmaceutical importance.[8] In this communication, we wish to report the preliminary results.

In our investigation of a PPh_3-mediated tandem reaction with compound **1a**, unexpectedly, we isolated a small amount of cyclization product **2a**, which indicates an unusual conjugation reaction of two electrophilic moieties (the benzyl halide and α,β-unsaturated carboxylic ester) and encouraged us to further explore this reaction in detail. Initially, the reactions were performed using a one-pot protocol at 80 °C using isopropyl acetate as the solvent, and the base effect was first examined. As shown in Table 1, the presence of base proved to be crucial to this reaction. Potassium *tert*-butoxide and organic bases like DBU and DMAP all gave a messy reaction and no desired product was observed (entries 1, 6 and 7). KOH or Na_2CO_3 gave promising yields, but substantial amounts of compound **3a** were obtained (entries 2 and 3), which probably resulted from the hydrolysis of the corresponding phosphonium ylides of the starting halide. To our delight, Cs_2CO_3 gave **2a** in a much higher yield, and only a trace amount of **3a** was detected by proton NMR (entry 5). Further evaluation of different solvents revealed that ethyl acetate is the solvent of choice, giving the desired product in 84% yield, and notably the formation of **3a** was completely suppressed (entry 13). Regarding the influence of the



Scheme 1 Reaction of electron-deficient olefins with alkyl halides.

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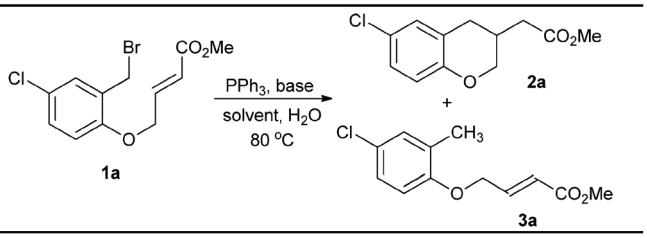
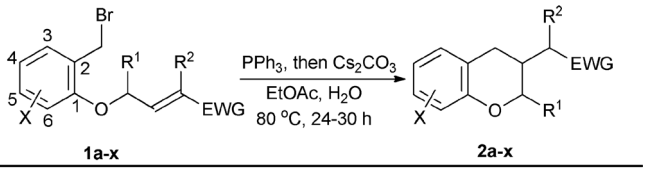
Table 1 Reaction optimization[a]



Entry	Base	Solvent	*t*/h	Yield[b] (%) **2a**/**3a**
1	*t*-BuOK	*i*-PrOAc	24	—[c]
2	KOH	*i*-PrOAc	18	50/20
3	Na_2CO_3	*i*-PrOAc	28	20/20
4	K_2CO_3	*i*-PrOAc	15	65/16
5	Cs_2CO_3	*i*-PrOAc	28	75/–
6	DBU	*i*-PrOAc	24	—
7	DMAP	*i*-PrOAc	24	—
8	Cs_2CO_3	DCE	21	53/13
9	Cs_2CO_3	CH_3CN	24	39/–
10	Cs_2CO_3	Dioxane	24	46/51
11	Cs_2CO_3	*t*-BuOH	21	—
12	Cs_2CO_3	*n*-BuOAc	24	71/–
13	Cs_2CO_3	EtOAc	24	84/–
14[d]	Cs_2CO_3	EtOAc	24	51/32
15[e]	Cs_2CO_3	EtOAc	25	87/–

[a] **1a** (0.3 mmol), PPh_3 (0.36 mmol), base (0.9 mmol), H_2O (2.5 equiv.), solvent (4 mL). [b] **2a** + **3a**, ratios were determined by ^1H NMR of the crude product. [c] Trace was detected by ^1H NMR. [d] With 10 equiv. of water. [e] Pre-mixing of **1a** (0.3 mmol) and PPh_3 (0.45 mmol) in EtOAc (4 mL) at 60 °C for 5 h, then Cs_2CO_3 (0.9 mmol), water (2.5 equiv.), and EtOAc (2 mL), at 80 °C.

Table 2 Reaction scope[a]



1a-x **2a-x**

Entry	X	R^1,R^2	EWG	Prod.	Yield[b] (%)
1	4-Cl	H, H	CO_2Me	**2a**	87
2	H	H, H	CO_2Me	**2b**	96
3	4-Me	H, H	CO_2Me	**2c**	93
4	4-OMe	H, H	CO_2Me	**2d**	92
5	5-OMe	H, H	CO_2Me	**2e**	72
6	6-F	H, H	CO_2Me	**2f**	92
7	4-Br	H, H	CO_2Me	**2g**	83
8	3,4-Benzo	H, H	CO_2Me	**2h**	63
9	5,6-Benzo	H, H	CO_2Me	**2i**	97
10	H	Me, H	CO_2Me	**2j**	96[c]
11[d]	H	H, Me	CO_2Et	**2k**	79[e]
12	4-Br	H, H	CO_2Et	**2l**	79
13	H	H, H	$CO_2{}^tBu$	**2m**	90
14	H	H, H	CON(Me)OMe	**2n**	83
15[f]	H	H, H	COPh	**2o**	82
16[f]	4-Me	H, H	COPh	**2p**	87
17[f]	H	H, H	CO(2-thienyl)	**2q**	77
18	H	H, H	CN	**2r**	93
19[g]	H	H, H	CN	**2r**	91
20	4-Br	H, H	CN	**2s**	86

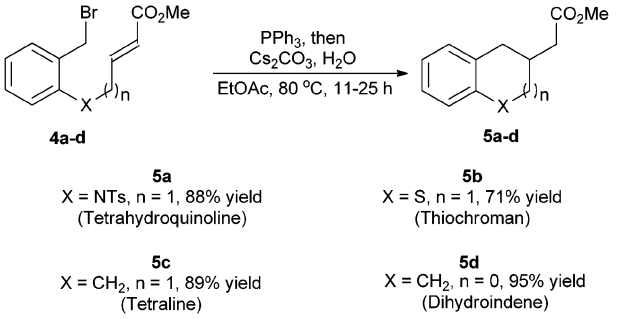
[a] Pre-mixing of **1** (0.3 mmol) and PPh_3 (0.45 mmol) in EtOAc (4 mL) at 60 °C, then Cs_2CO_3 (0.9 mmol), H_2O (2.5 equiv.), and EtOAc (2 mL), at 80 °C. [b] Isolated yield. [c] dr = 1.3/1. [d] With PMe_3. No **2k** was produced with PPh_3. [e] dr = 1.7/1. [f] 20 equiv. of H_2O, 40 °C. [g] With the *Z*-isomer of **1r**.

amount of water, 2.5 equivalents of water proved to be optimal.[9] The reaction without additional water is slower, while adding excess amounts of water led to severe hydrolysis of the phosphonium salt of **1a** forming **3a** (32%, entry 14). On the other hand, lowering the temperature to 40 °C or 60 °C decreased the yield.[9] However, the isolated yield of **2a** can be further increased slightly to 87% by pre-mixing the halide and phosphine for 5 h at 60 °C before the addition of base (entry 15). It is worth mentioning that in the current reaction no Morita–Baylis–Hillman (MBH)-type alkylation product was obtained, though both the phosphine and the α,β-unsaturated ester group were present in the reaction.[10]

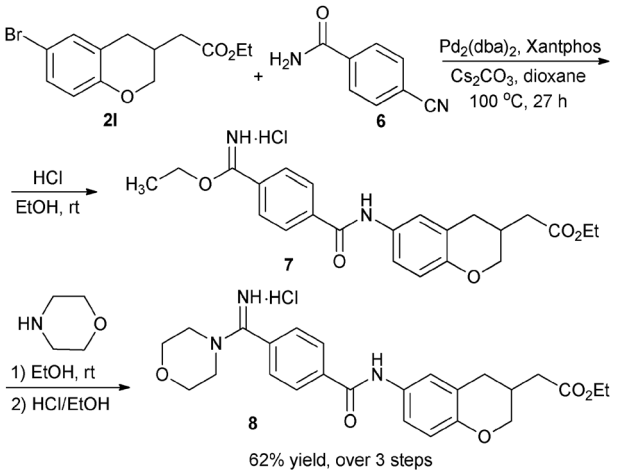
Under the optimized reaction conditions, the reaction scope was evaluated next. As shown in Table 2, functional groups such as –Cl, –Br, –OMe, –F, ketone, ester, amide, and nitrile are all well tolerated in this reaction, giving the desired product in good to high yields. Electron-donating groups on the benzene ring generally gave better yields (entries 1–4), but the 5-methoxy substituted bromide **1e** afforded a little bit of lower yield due to its instability (72%, entry 5). Fused tricyclic benzochromans can also be synthesized using the current reaction (entries 8 and 9). In the case of **1k**, the use of PPh_3 only gave the hydrolysis product **3k** and no desired product **2k** was isolated, which can be attributed to the sensitivity of the PPh_3 group to the steric hindrance on the double bond. Nevertheless, less steric and more nucleophilic phosphines like PMe_3 can substantially alleviate this steric repulsion and improve the yield (entry 11). To our delight, apart from the carboxylic ester groups, the reaction also works well with other electron-withdrawing groups like ketone, amide, and nitrile (entries 14–20). Importantly, the yield is almost independent of the configuration of the double bond in the substrate (entry 18 *vs.* 19). In addition, the corresponding chloride and mesylate of **1b** also reacted well and furnished the desired chroman product **2b** in good yield.[9]

Encouraged by these results, we moved to the extension of this reaction to the syntheses of other benzocycles like thiochromans, tetrahydroquinolines, tetralines, and dihydroindenes, which are useful synthetic intermediates and common structures in many molecules that exhibit various biological activities.[5a,8] Gratifyingly, as exemplified in Scheme 2, the approach works well with all these substrates, delivering the desired benzocyclic products in good to high yields.[9] Notably, the present reaction provides a new C3–C4 disconnection method in the retro-synthetic analysis of these benzoheterocycles.[8a,11]

The current reaction is potentially useful in organic synthesis. For example, product **2r** is a key intermediate for the synthesis of a series of dyslipidemia-modulating agents. The patent method required seven steps to make this compound, starting from salicylaldehyde.[12]



Scheme 2 Extension to the syntheses of chroman analogues.



Scheme 3 Synthesis of a potent glycoprotein IIb–IIIa antagonist.

To further demonstrate the synthetic potential of this reaction, a route based on product **2l** was designed for the synthesis of compound **8** (Scheme 3), the (*S*)-isomer (MS-180) of which is a potential drug selected for clinical evaluation for the treatment and prevention of thrombosis (glycoprotein IIb–IIIa antagonist) in patients.[13] Palladium-catalyzed coupling of **2l** with amide **6**, followed by treatments in ethanol in the presence of anhydrous hydrogen chloride and later with morpholine, gave the benzimidamide intermediate. Subsequent precipitation in dry HCl–EtOH delivered the target product **8** in 62% yield over three steps. It is worth mentioning that the overall yield for **8** from 4-bromosalicylaldehyde is 42%, while in comparison, the overall yield reported in the literature is *ca.* 17%, starting from much more expensive 6-nitrochroman-4-one.[13]

In summary, a phosphine-mediated intramolecular conjugation of alkyl halides with electron-deficient C=C double bonds has been successfully developed. The reaction conditions are mild and no conversion of the alkyl halide to the organometallic reagent is required. This direct connection of two electrophilic moieties provides a new and facile synthetic route for the preparation of chroman derivatives, and can also be extended to the construction of other relevant analogues such as tetrahydroquinolines, thiochromans, and tetralines. Based on this reaction, a short synthetic route to a potent glycoprotein IIb–IIIa antagonist has also been developed. Application of the current method in natural product synthesis and the development of an asymmetric version are currently ongoing in our laboratory.

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