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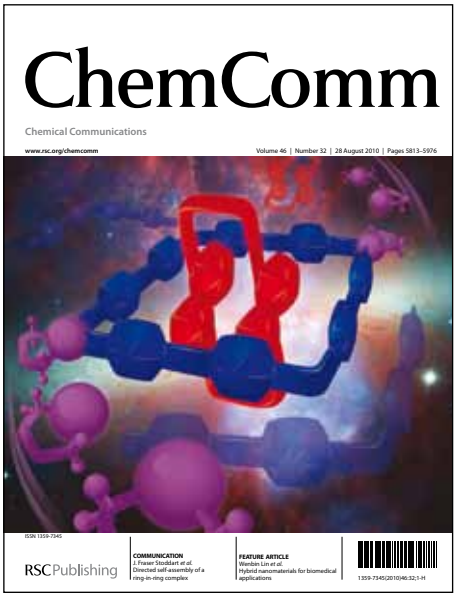

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ARTICLE TYPE

Direct β-Acylation of 2-Arylidene-1,3-indandiones with Acyl Chlorides Catalyzed by Organophosphanes †

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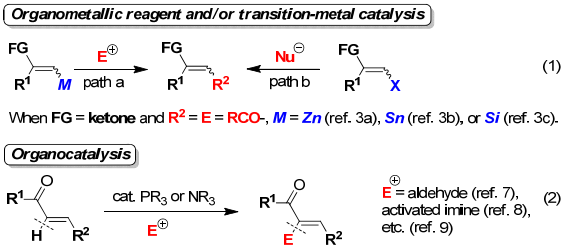
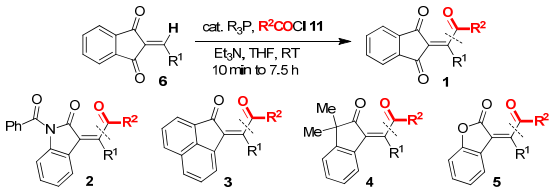
We have developed an organophosphane-catalyzed direct β-acylation on a series of conjugated systems bearing ketone, amide and ester funcitonalities using acyl chlorides as trapping reagents. A wide variety of highly functional ketone derivatives were generated efficiently in very mild condition with high yields according to our protocol. Our adducts can even be utilized as important building blocks for the synthesis of functional tri/tetracyclic pyridazine derivatives.

The exploration of direct transformation of C-H bonds of electron-deficient alkenes into C-C bonds attracts chemists much attention because it is considered as a very challenging task and has many benefits in organic synthesis.[1] A lot of efforts have been taken to develop efficient methods for generation of C-C bonds (sp^2-sp^2 or sp^2-sp^3) using organometallic reagents[2,3a] or even utilizing transition-metal catalyzed coupling reactions[2,3b,3c] with potential electrophiles. Among all the developed protocols, organozinc reagents turned out to be the most practical one with high functional-group tolerance such as ketone or aldehyde functionalities.[3a] However, the activation of nucleophiles as organometallic species (path a) or electrophiles with an iodo- or bromo- substitution (path b) is normally required, which may further limit the substrate scope when sensitive functional groups are present (equation 1, Scheme 1).[2-3] Recently, direct oxidative acylation of aryl-substituted olefins[4], arenes[5], or heteroarenes[6] with aromatic aldehydes was demonstrated as an interesting approach to install ketone functionality. However the extension or study of this similar concept with electrophilic alkenes is still unrevealed and difficult probably due to the electron-deficient properties of olefins. The Morita-Baylis-Hillman reaction, which is one of the most powerful methods for C-C bond formation, has many important applications in synthetic chemistry (equation 2).[7-9] It allows direct functionalization on α-position of α,β-unsaturated ketones or esters with different electrophiles such as aldehydes and imines, thus making synthesis shorter and more efficient.[7-9] To our surprise, it is still impossible to directly install an acyl group at β-position of an electrophilic olefin with the retention of its original functionalities. Herein, we report the preparation of highly conjugated ketone derivatives **1-5** starting from α,β-unsaturated ketone, ester, or amide derivatives **6-10** and acyl chlorides **11** catalyzed by organophosphane in the presence of Et_3N via direct β-acylation (Scheme 2). To the best of our knowledge, it is the first time to directly install a ketone functionality at β-position of electrophilic olefins using an organophosphane as the organocatalyst.



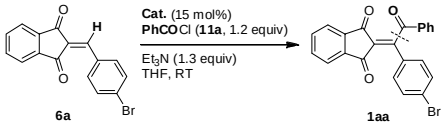
Scheme 1 Functionalization of electrophilic alkenes.



Scheme 2 β-Acylation of electrophilic alkenes **6-10**: synthesis of **1-5**.

At first, 2-(4-bromobenzylidene)-1,3-indandione (**6a**) and benzoyl chloride (**11a**, 1.2 equiv) were selected as testing substrates with different nucleophilic organocatalysts in the presence of Et_3N (1.3 equiv) in THF (Table 1). 1,4-Diazabicyclo[2.2.0]octane (DABCO) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), which are commonly used as nucleophilic catalysts, failed to catalyze our designed reaction (entries 1 and 2). We then turned our attention to use organophosphanes as catalysts. Triphenylphosphine also failed to promote the reaction even in 20 mol% catalytic loading (entry 3). When an organophosphane (15 mol%) with stronger nucleophilicity, such as Bu_3P, Et_3P, or iBu_3P, was employed as the catalyst, the expected adduct **1aa** was provided within 1 h in 40%, 85%, or 78% yield, respectively (entries 4-6). However, a bulky trialkyl organophosphane, such as Cy_3P, did not successfully catalyze the reaction (entry 7). To our delight, $MePPh_2$ (10 mol%) showed a very high catalytic ability for our expected reaction, and the desired adduct **1aa** was provided in 98% yield within 1 h (entries 9-10). Surprisingly, only the corresponding phosphorus zwitterion **12a** instead of **1aa** was afforded when 1.2 equiv of Bu_3P was used (entry 11 vs entry 4). This phenomenon was not observed in case of $MePPh_2$ (1.2 equiv), and the reaction of **6a** and **11a** in the presence of Et_3N proceeded smoothly at room temperature within 1 h to furnish **1aa** in 95% yield (entry 12).[10]

Table 1 Optimization of reaction conditions for the synthesis of **1aa** [a]

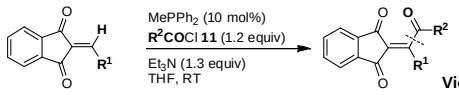


Entry	Cat.	Time (h)	Yield of **1aa** (%)[b]
1[c]	DABCO	1 (24)[d]	No reaction
2[c]	DBU	1 (24)[d]	No reaction
3[c]	Ph_3P	1 (24)[d]	No reaction
4	Bu_3P	1	40
5	Et_3P	1	85
6	iBu_3P	1 (2)[d]	78 (87)[e]
7	Cy_3P	1	No reaction
8	$EtPPh_2$	1 (2)[d]	75 (90)[e]
9	$MePPh_2$	1	99
10[f]	$MePPh_2$	1	98[g]
11[h]	Bu_3P	1 (12)[d]	0[i]
12[h]	$MePPh_2$	1	95

[a]Reactions were performed with **6a** (0.3 mmol) in anhydrous THF (1.5 mL) under nitrogen. [b]Determined by ^1H NMR analysis of the crude reaction mixture using Ph_3CH as an internal standard. [c]20 mol% of catalyst was used. [d]The reaction time was prolonged to 2, 12 or 24 h. [e]The NMR yield was investigated within 2 h. [f]10 mol% of $MePPh_2$ was used. [g]Isolated yield. [h]1.2 equivalent of Bu_3P or $MePPh_2$ was used. [i]Only the corresponding phosphorus zwitterion **12a** (98% yield) resulting from **6a** and Bu_3P was obtained.

The broad reaction scope of our optimized protocol for substrates **6** with **11** is demonstrated in Table 2. It shows that, under our catalytic reaction condition (10 mol% of $MePPh_2$), direct β-acylation of **6** with various acyl chlorides **11** was realized successfully (Table 2). The reaction of **6a** and aryl-substituted acyl chlorides **11a-f** (1.2 equiv) in the presence of $MePPh_2$ (10 mol%) and Et_3N (1.3 equiv) took place efficiently at room temperature (0.5 to 2 h), leading to the corresponding acylated adduct **1aa-1af** in excellent yields (entries 1-6). An aryl-subsitituted acyl chloride with an electron-donating group, such as **11g**, is less reactive than **11a-f** towards **6a** according to the same protocol, providing the expected adduct **1ag** in 97% yield (7.5 h; entry 7). Heteroaryl-substituted acyl chlorides, such as **11h** and **11i**, also worked nicely with **6a** within 3 or 5 h to furnish the corresponding products **1ah** and **1ai** in good yields (entries 8 and 9). It is necessary to increase the catalyst loading of $MePPh_2$ (50 mol%) when alkyl-substituted acyl chlorides such as **11j**, **11k**, and **11l** were employed, and the corresponding adducts **1aj**, **1ak** and **1al** were afforded in good to high yields within 0.5 or 1 h (entries 10-12). Interestingly, trifluoroacetic anhydride (**11m**) was very reactive towards **6a** in the presence of 10 mol% of $MePPh_2$ and Et_3N (1.3 equiv), and the reaction proceeded successfully and efficiently to give the corresponding adduct **1am** (80%, 10 min; entry 13). Not only a wide range of acyl chlorides **11a-m** can be applied with **6a**, but also other different β-aryl or β-heteroaryl substituted Michael acceptors **6b-m** can be utilized successfully according to the same protocol (entries 14-25). All the corresponding acylated adducts **1ba-1ha** starting from **6b-h** were generated within 0.5 to 3 h in good to excellent yields, and remarkably an aldehyde funcitonality can be tolerated successfully in case of **1ea** (entries 14-20). When less reactive substrates, such as **6i-l**, were treated with **11a**, 15 mol% $MePPh_2$ was necessary to efficiently promote our designed reactions (entries 21-24).

Table 2 Organocatalytic synthesis of **1** via direct β-acylation.[a]



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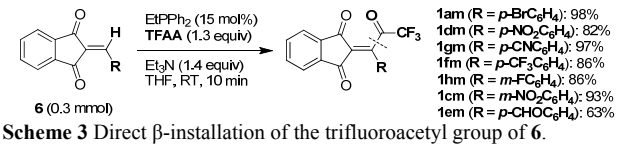
Entry	R^1	R^2	Time (h)	**1** (%)[b]
1	*p*-BrPh **6a**	Ph **11a**	2	**1aa**, 98
2	**6a**	*o*-ClPh **11b**	1	**1ab**, 97
3	**6a**	*m*-ClPh **11c**	0.5	**1ac**, 98
4	**6a**	*p*-ClPh **11d**	0.5	**1ad**, 93
5	**6a**	*o*-BrPh **11e**	0.5	**1ae**, 97
6	**6a**	*p*-BrPh **11f**	0.5	**1af**, 97
7	**6a**	*p*-MeOPh **11g**	7.5	**1ag**, 97
8[c]	**6a**	2-Furyl **11h**	3	**1ah**, 71 (90)[d]
9	**6a**	2-Thienyl **11i**	5	**1ai**, 87
10[e]	**6a**	*i*Pr **11j**	1	**1aj**, 79
11[e]	**6a**	*c*Hexyl **11k**	1	**1ak**, 79
12[e]	**6a**	Nonanyl **11l**	0.5	**1al**, 57
13	**6a**	CF_3[f] **11m**	10 min	**1am**, 80
14	Ph **6b**	**11a**	1	**1ba**, 92[g]
15	*m*-NO_2Ph **6c**	**11a**	3	**1ca**, 75 (90)[d]
16	*p*-NO_2Ph **6d**	**11a**	1	**1da**, 97
17	*p*-CHOPh **6e**	**11a**	0.5	**1ea**, 97
18	*p*-CF_3Ph **6f**	**11a**	1	**1fa**, 97
19	*p*-CNPh **6g**	**11a**	0.5	**1ga**, 99
20	*m*-FPh **6h**	**11a**	1	**1ha**, 91
21[c]	*p*-MePh **6i**	**11a**	2	**1ia**, 99
22[c]	*p*-MeOPh **6j**	**11a**	3	**1ja**, 94
23[c]	2-Furyl **6k**	**11a**	7	**1ka**, 33 (71)[d]
24[c]	2-Thienyl **6l**	**11a**	7	**1la**, 53 (92)[d]
25	3-Pyridinyl **6m**	**11a**	1	**1ma**, 94

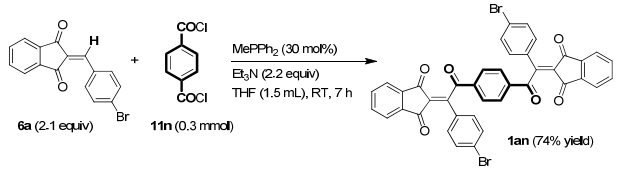
[a]Reactions were performed with **6** (0.3 mmol) in anhydrous THF (1.5 mL) under nitrogen. [b]Isolated yield. [c]15 mol% of $MePPh_2$ was used. [d]Recovered yield. [e]50 mol% of $MePPh_2$ was used. [f]Trifluoroacetic anhydride (TFAA) was used. [g]The structure of **1ba** was determined by X-ray analysis.[11]

Fluorinated organic compounds are important substrates, and therefore many related studies as well as development of new synthetic methods are growing up rapidly.[12] After our careful optimization of reaction conditions, $EtPPh_2$ was the best catalyst for the reactions of **6** and TFAA, and all the corresponding adducts **1** with the trifluoroacetyl group were provided very efficiently in good to excellent yields (Scheme 3).



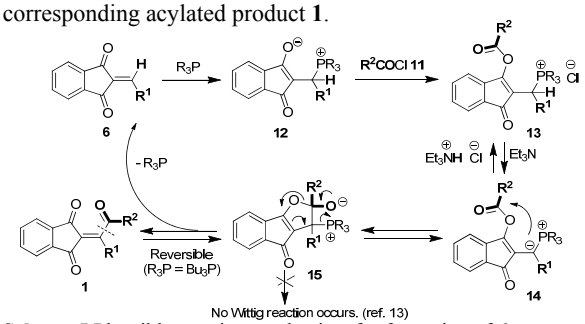
Scheme 3 Direct β-installation of the trifluoroacetyl group of **6**.

Furthermore, our developed protocol allowed direct double β-acylation of **6**. A three-component reaction of **6a** (2.1 equiv) and **11n** (0.3 mmol) in the presence of $MePPh_2$ (30 mol%) and Et_3N (2.2 equiv) underwent smoothly within 7 h at room temperature, furnishing a complex molecule **1an** in 74% yield (Scheme 4).



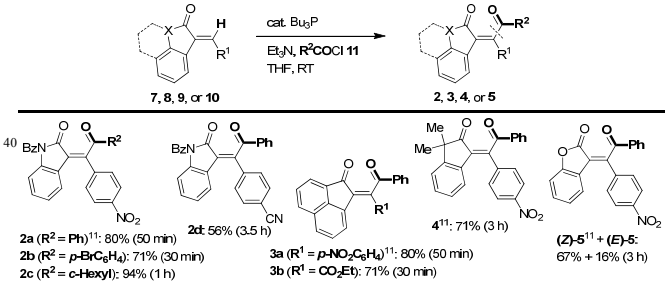
Scheme 4 Synthesis of **1an** via a three-component reaction.

According to experimental results[10] (Tables 1-2, Schemes 3-4), a plausible reaction mechanism was proposed (Scheme 5). First, the Michael addition of organophosphane (R_3P) towards **6** took place, giving rise to the corresponding zwitterion **12**. The intermediate **12** was acylated with an acyl chloride **11**, leading to the formation of **13**. Then deprotonation of **13** by Et_3N happened, and the resulting ylide **14** underwent an intramolecular 1,2-addition reaction towards the ester group followed by elimination of enolate and then regeneration of R_3P, affording the corresponding acylated product **1**.

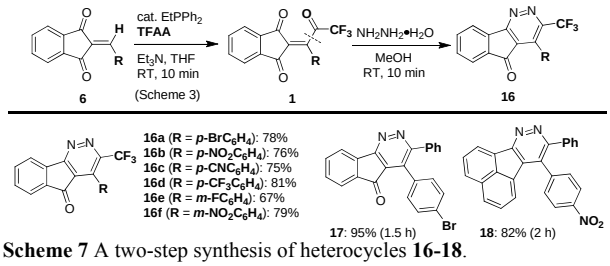


Scheme 5 Plausible reaction mechanism for formation of **6**.

Remarkably, our synthetic protocol can be applied in the preparation of β-acylated adducts **2-5** successfully in our preliminary studies (Scheme 6). After careful optimization (see ESI), Bu_3P was chosen as the organocatalyst (10 or 20 mol%). Aryl and cyclohexyl acyl chlorides **11** were reacted efficiently with 3-arylidene oxindoles **7a-b** to afford the corresponding products **2a-d** in 56-94% yields (0.5-3.5 h). Acenaphthyl derived arylidene analogue **8a** also worked very well according to our protocol to provide **3a** in 80% yield (50 min). Interestingly, acenaphthyl alkylidene containing an ester group **8b** was well tolerated too, affording the product **3b** in 71% yield (0.5 h). The substrate scope was further extended by using 2-indanone or 2-coumaranone derived arylidene (**9** or **10**) to furnish the corresponding product **4** or **5**, respectively (71% or 83%; 3 h). It is interesting that, in the case of **10**, both geometrical isomers of the products (*Z*)-**5a** (67%) and (*E*)-**5a** (16%) were obtained.



Scheme 6 Synthesis of **2-5** via direct β-acylation (see ESI).



Scheme 7 A two-step synthesis of heterocycles **16-18**.

Next, the utility of the products **1** for further derivatization is demonstrated. In this direction the products **1** were allowed to react with hydrazine hydrate for a double condensation reaction. The reactions proceeded smoothly within 10 min at ambient temperature, and the resulting pyridazines **16** were obtained in moderate to high yield (Scheme 7). Other adducts such as **1aa** and **3a** were also employed to provide **17**[11] and **18**[11] within 1.5 h to 2 h in high yields. It is worth mentioning that pyridazines constitute important structural motif representing many biologically active compounds.[14]

In conclusion, we have demonstrated a novel strategy for the metal-free, catalytic direct β-acylation on the simple conjugated systems *via* organophosphanes. A diverse range of α,β-unsaturated ketone, ester or amide derivatives have been successfully applied, which provided an array of corresponding β-acylated products in good to excellent yields. With this interesting result, we developed very convenient two-step synthesis for the drug potential materials, pyridazines. Further extensions of this work are currently underway in our laboratories.

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Notes and references

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† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/b000000x/

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