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Acylperoxycoumarins as *ortho*-C–H Acylating Agent *via* a Palladium(II)-Catalyzed Redox-Neutral Process

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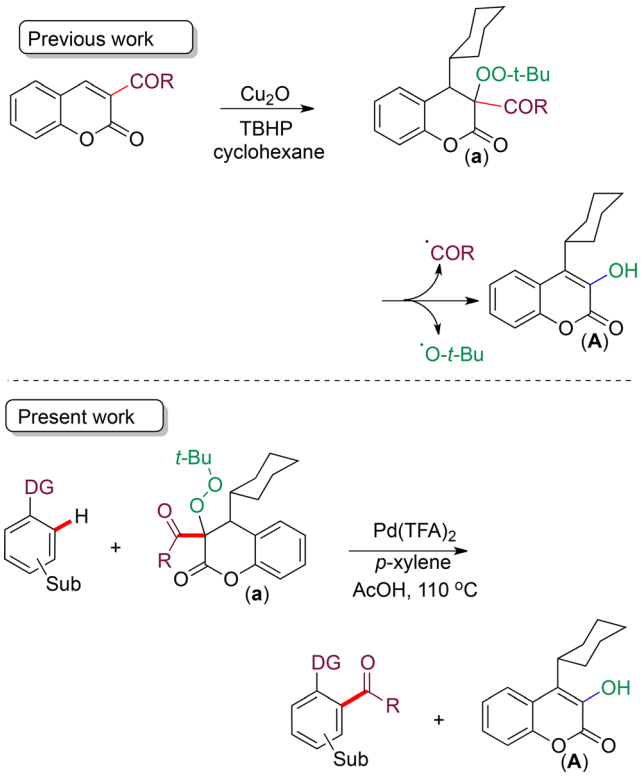
Abstract: An unprecedented palladium(II)-catalyzed biomimetic aliphatic acyl (-COR) group transfer was observed from acyl-α-peroxycoumarins to the *ortho* C–H sites of directing arenes. Here, the C–H activation is associated with a concomitant acyl group transfer *via* a Pd(II)-catalyzed, redox-neutral process. While methods for *ortho* aroylation (-COAr) are well documented *ortho* acylation (-COR) processes are scarce, hence the present redox-neutral method is most ideal for *o*-acylation of directing substrates.

Keywords: acyl group transfer; C–H activation; palladium catalysis; redox-neutral process

Transfer of various functional groups from one molecule to another is not uncommon in the literature.[1] Earlier our group reported on "thiocyanate transfer agents" *viz.* acyl isothiocyanates which transfer isothiocynate to various electrophilic sites such as α-bromo ketones or benzyl bromides in the presence of a tertiary amine.[2] However, intermolecular group transfer in any C–H functionalizations is unfamiliar so far. Recently, we have achieved two cycloalkylation-peroxidation strategies for coumarins, one involving metal-free conditions and the other using a copper(I) salt in which *tert*-butyl hydroperoxide (TBHP) acted as an oxidant as well as a reactant.[3] The acyl-α-peroxy product, i.e., 3-acetyl-3-(*tert*-butylperoxy)-4-cyclohexylchroman-2-one (**a**) [obtained by reacting 3-acetylcoumarin, cyclohexane and TBHP in the presence of catalyst Cu_2O[3a]] slowly decomposed on prolonging the reaction time, but the isolated product is sufficiently stable at room temperature.[3a] Thermogravimetric analysis (TGA) data of 3-acetyl-3-(*tert*-butylperoxy)-4-cyclohexylchroman-2-one (**a**) showed that decomposition started only above 170 °C (see the Supporting Information). No explosion was observed in any of the reactions even when carried out on a 2 mmol scale, thus the reagent is safe to handle. A careful scrutiny of the decomposed product revealed it to be a 4-cyclohexyl-3-hydroxy-2*H*-chromen-2-one (**A**), which is obtained *via* the cleavage of both the peroxo (O–O) and C–C bonds of (**a**) (Scheme 1). Since the acyl-α-peroxycoumarin (**a**) has an inbuilt thermally labile peroxy (O–O) linkage, homolytic cleavage of it will trigger the cleavage of an α-COR group generating an acyl radical (COR). Thus, the *in-*



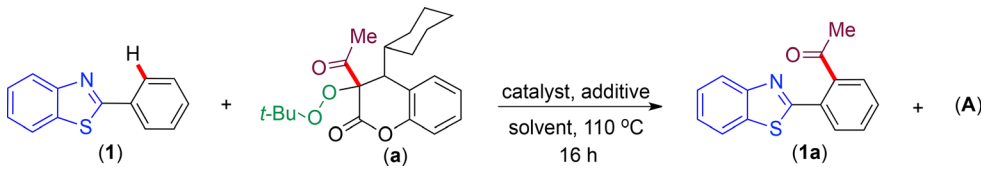
Scheme 1. Coumarin as acyl transfer reagent.

situ released acyl radical (COR) can be trapped and utilized for the *o*-acylation of directing substrates *via* a metal-mediated C–H functionalization process. Thus, the substrate (**a**) can be envisaged as a redox-neutral reagent in a Pd-catalyzed directed *o*-acylation *via* C–H activation.

Various directing groups along with different aroyl surrogates *viz.* aldehydes, benzyl alcohols, α-keto acids, benzil derivatives, benzylamines, alkenes, alkynes and even inert alkylbenzenes have been employed for *ortho*-aroylations.[4] The majority of these strategies are successful for the synthesis of aryl (aromatic) ketones. However, syntheses of alkyl (aliphatic) ketones *via* ligand-directed C–H activation are fewer in number. Due to the lower stability of acyl radicals compared to aroyl radicals, they are less explored towards substrate directed *o*-acylations. Recently, a few aliphatic aldehydes and aliphatic diketones have been employed as the *o*-acyl sources with limited examples using a slight excess of oxidant (TBHP) in a sealed tube.[5] To avoid the use of excess oxidants and specialized reaction conditions, redox-neutral C–H functionalization strategies have been developed by various groups.[6] Our group has made significant contributions in the area of directing group-assisted C–H functionalizations of various directing arenes, specifically 2-arylbenzothiazoles.[7] Therefore, 2-arylbenzothiazole was chosen as the model substrate to elucidate our concept of redox-neutral *o*-acylation using acyl-α-peroxycoumarin (**a**) as the acyl source as well as an internal oxidant.

To verify our proposed hypothesis, 2-phenylbenzothiazole (**1**) and 3-acetyl-3-(*tert*-butylperoxy)-4-cyclohexylchroman-2-one (**a**) were reacted in the presence of 10 mol% of $Pd(OAc)_2$ in toluene at 110 °C. A new product was isolated; spectroscopic analysis of which showed the presence of a singlet (Me group) at 2.40 ppm in its ^{1}H NMR and a peak at 204.0 ppm in its ^{13}C NMR suggesting the incorporation of an acyl (-COMe) group in the product. Further spectroscopic analysis revealed its structure to be 1-{2-(benzo[*d*]-thiazol-2-yl)-phenyl}ethanone (**1a**). The product (**1a**) was however obtained in 21% isolated yield (Table 1, entry 1) along with the formation of a by-product (**A**) (Scheme 1).[3a] The addition of AcOH is reported to facilitate the homolytic cleavage of organic peroxides.[3b] The yield of product (**1a**) improved up to 49% when 0.5 mL (35 equiv.) of AcOH was added to the reaction mixture under otherwise identical conditions (Table 1, entry 2). To achieve the best yield for this *o*-acylation process, various other reaction parameters such as solvent, catalyst and additives were varied. The use of polar solvents such as 1,4-dioxane (32%), DMF (0%), and DMSO (0%) under identical reaction conditions were not so favourable (Table 1, entries 3–5) whereas among the non-polar solvents such

Table 1. Screening of the reaction conditions.[a]

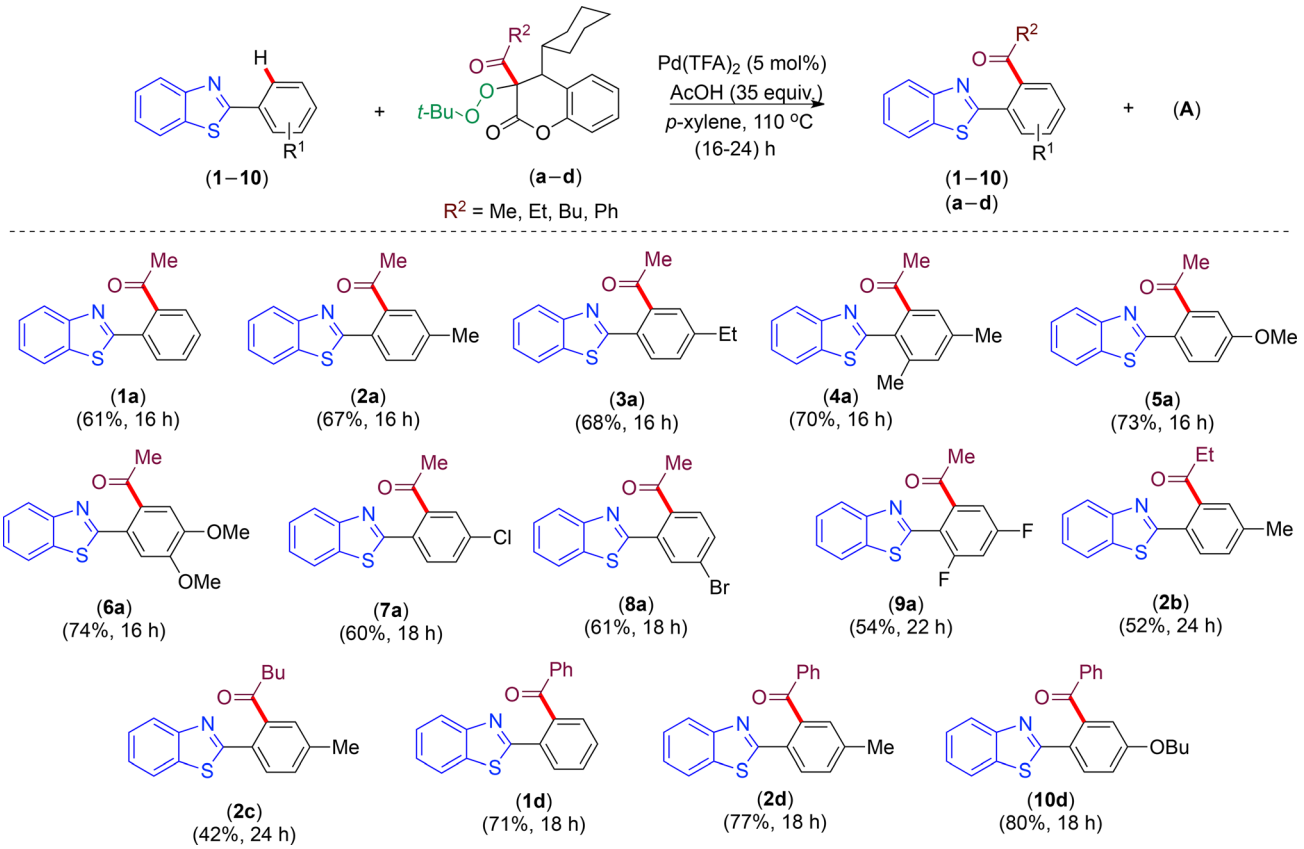


Entry	Catalyst (mol%)	Additive	Solvent	Yield [%][b]
1	$Pd(OAc)_2$ (10.0)	–	toluene	21
2	$Pd(OAc)_2$ (10.0)	AcOH	toluene	49
3	$Pd(OAc)_2$ (10.0)	AcOH	dioxane	32
4	$Pd(OAc)_2$ (10.0)	AcOH	DMF	0
5	$Pd(OAc)_2$ (10.0)	AcOH	DMSO	0
6	$Pd(OAc)_2$ (10.0)	AcOH	CyH	43
7	$Pd(OAc)_2$ (10.0)	AcOH	DCE	38
8	$Pd(OAc)_2$ (10.0)	AcOH	PhCl	53
9	$Pd(OAc)_2$ (10.0)	AcOH	*p*-xylene	59
10	$Pd(TFA)_2$ (10.0)	AcOH	*p*-xylene	63
11	$PdCl_2$ (10.0)	AcOH	*p*-xylene	14
12	$PdBr_2$ (10.0)	AcOH	*p*-xylene	10
13	$Pd(TFA)_2$ (10.0)	PTSA	*p*-xylene	31
14	$Pd(TFA)_2$ (10.0)	TFA	*p*-xylene	44
15	$Pd(TFA)_2$ (10.0)	PviOH	*p*-xylene	trace
16	**$Pd(TFA)_2$ (5.0)**	**AcOH**	***p*-xylene**	**61**
17	$Pd(TFA)_2$ (15.0)	AcOH	*p*-xylene	64

[a] *Reaction conditions:* 2-phenylbenzothiazole (**1**) (0.25 mmol), (**a**) (0.25 mmol), additive (0.5 mL, 35 equiv.) and solvent (1 mL) at 110 °C for 16 h.
[b] Yields of the isolated pure product.

as cyclohexane (43%), DCE (38%), chlorobenzene (53%) and *p*-xylene (59%) tested, the later gave the best yield of *o*-acylated product (**1a**) (Table 1, entries 6–9). Furthermore, using *p*-xylene as the solvent and AcOH as an additive various Pd catalysts were assessed. The use of 10 mol% $Pd(TFA)_2$ was found to be the best compared to other Pd catalysts such as $PdCl_2$ (14%) and $PdBr_2$ (10%) (Table 1, entries 10–12) tested. Other acid additives, *viz.* PTSA, TFA and PivOH (Table 1, entries 13–15), screened were found to be less effective compared to AcOH (Table 1, entry 10). Furthermore, on reducing the catalyst loading from 10 to 5 mol% the yield of the product remained virtually unaltered (61%) (Table 1, entry 16). A marginal improvement in the yield (64%) was observed when the catalyst loading was increased to 15 mol% (Table 1, entry 17). Therefore, the acyl transfer from acyl-α-peroxycoumarin (**a**) to the directing substrate (**1**) was best achieved using 5 mol% of $Pd(TFA)_2$ in the presence of additive AcOH (0.5 mL, 35 equiv.) in *p*-xylene solvent at 110 °C (Table 1, entry 16).

Delighted by this novel acyl transfer process, we further explored its scope with other 2-arylbenzothiazoles. Acyl-α-peroxycoumarin (**a**) smoothly transferred the acyl group to the *ortho* position of 2-arylbenzothiozles containing electron-donating as well as electron-withdrawing substituents (Scheme 2). 2-Arylbenzothiazoles having weakly electron-donating substituents such as *p*-Me (**2**), *p*-Et (**3**) and 2,4-di-Me (**4**) provided moderate yields of the desired products (**2a**, 67%), (**3a**, 68%) and (**4a**, 70%). However, substrates possessing strongly electron-donating substituents such as *p*-OMe (**5**) and 3,4-di-OMe (**6**) in the 2-aryl ring of benzothiazole afforded *o*-acylated products (**5a**) and (**6a**) in 73% and 74% yields, respectively. 2-Arylbenzothiazoles having moderately electron-withdrawing substituents such as *p*-Cl (**7**), *m*-Br (**8**) and 2,4-di-F (**9**) in their 2-aryl rings provided their corresponding *o*-acylated products (**7a**), (**8a**) and (**9a**) in 60%, 61% and 54% yields, respectively. 2-Arylbenzothiazoles possessing strongly electron-withdrawing groups such as *m*-NO_2 and *p*-CN in their 2-aryl ring failed to provide the desired *o*-acylated products. This may be due to the difficulty in electrophilic palladation of the electron-deficient aryl rings. Electron-rich 2-arylbenzothiazoles (**2**–**6**) provided better yields of their *o*-acylated products compared to electron-deficient 2-arylbenzothiazoles, which is due to the facile electrophilic palladation of electron-rich substrates.



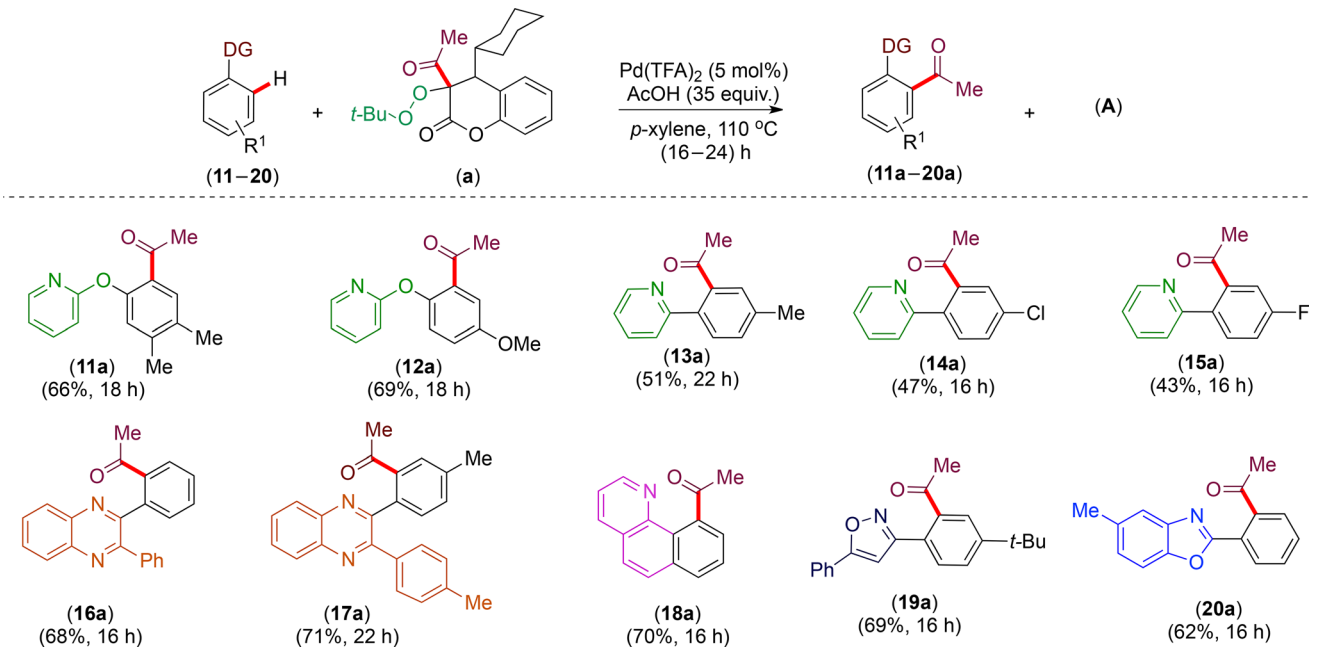
Scheme 2. Scope of the *o*-acylation of 2-arylbenzothiazoles *via* group transfer. *Reaction conditions:* 2-arylbenzothiazoles (**1**–**10**) (0.25 mmol), (**a**–**d**) (0.25 mmol), AcOH (0.5 mL, 35 equiv.) in *p*-xylene (1 mL) at 110 °C for 16–24 h. Yields of the isolated pure products.

Single regioisomeric products (**6a**) and (**8a**) were observed at the less sterically hindered *ortho* position for *meta*-substituted benzothiazoles (**6**) and (**8**) because of the preferential palladation at these sites.

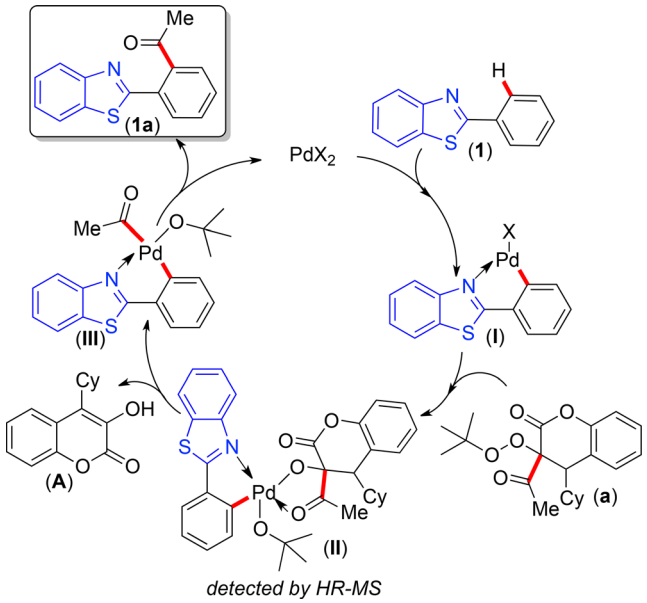
In a pursuit to see whether this methodology is applicable for the transfer of other acyl groups, acyl-α-peroxycoumarins possessing α-COEt (**b**), α-COBu (**c**) and α-COPh (**d**) substituents were reacted with benzothiazoles (**1**), (**2**) and (**10**) under the optimized reaction conditions (Scheme 2). Acyl-α-peroxycoumarins (**b**) and (**c**) successfully transfer their acyl groups to the *ortho* position of (**2**) providing acylated products (**2b**) and (**2c**) in 52% and 42% yields, respectively. Again, aroyl-α-peroxycoumarin (**d**) smoothly transferred the aroyl (-COPh) group to substrates (**1**), (**2**) and (**10**) affording their desired *o*-aroylated products (**1d**), (**2d**) and (**10d**), respectively, in 71%, 77%, and 80% yields. The higher yield of product obtained during aroyl group (-COPh) (**d**) transfer as compared to acyl groups (**a**–**c**) is due to the better stability of the aroyl radical (•COPh) compared to acyl radicals (•COR).

The scope and generality of this group transfer cum *o*-acylation protocol was further extended to various nitrogen chelated directing arenes such as, phenoxypyridine, 2-arylpyridine, 2,3-diarylquinoxaline, 3,5-diarylisooxazole, benzo[*h*]quinoline, and 2-phenylbenzoxazole (Scheme 3). The same optimized reaction conditions when applied to phenoxypyridines (**11**) and (**12**) afforded their *ortho*-acylated products (**11a**) and (**12a**) in 66% and 69% yields, respectively. The well investigated 2-arylpyridines (**13**), (**14**) and (**15**) also underwent directed acylation leading to the formation of their corresponding *o*-acylated products (**13a**), (**14a**) and (**15a**) in modest yields. Interestingly, directing arene 2,3-diarylquinoxalines (**16**) and (**17**) afforded exclusive mono-*o*-acylated products (**16a**) and (**17a**) in moderate yields (Scheme 3). This method is equally compatible with other directing groups such as benzo[*h*]quinoline (**18**), 3,5-diarylisoxazole (**19**) and 2-arylbenzoxazole (**20**) demonstrating the versatility of this acyl transfer process (Scheme 3).

When substrate (**1**) was treated under the optimized reaction conditions in the presence of a stoichiometric amount of radical scavenger (2,2,6,6-tetramethylpiperidine 1-oxyl, TEMPO), the yield of the product (**1a**) remains virtually unaltered. This experiment confirms the non-radical nature of the acylation process. So as per our assumption, generation of the acyl radical from acyl-α-peroxycoumarin (**a**) is not the actual path. The reaction proceeds *via* initial insertion of Pd(II)-arene complex (**I**) to the peroxy (O–O) linkage *via* an oxidative addition generating species (**II**).[8] Formation of species (**II**) was further confirmed *via* the HR-MS analysis of the reaction aliquot (see the Supporting Information). In the next step species (**II**) is converted to an acyl-palladium species (**III**) *via* the expulsion of a hydroxycoumarin (**A**). The product (**A**) has been isolated and its structure was confirmed by spectroscopic analysis as well as comparison with the reported literature data of the compound.[3a] In the final step *o*-acylated benzothiazole (**1a**) was



Scheme 3. Scope of directing arenes in the *o*-acylation reaction *via* group transfer. *Reaction conditions:* directing arenes (**11**–**20**) (0.25 mmol), (**a**) (0.25 mmol), AcOH (0.5 mL, 35 equiv.) in *p*-xylene (1 mL) at 110 °C for 16–22 h. Yields of the isolated pure products.



Scheme 4. Plausible mechanism for acyl transfer.

formed with the regeneration of Pd(II) catalyst (Scheme 4).

In conclusion, we have for the first time demonstrated an acyl group transfer *via* directed C–H activation. Interestingly, this is a unique redox-neutral process where the internal peroxy group not only served as an oxidant but also triggers the release of an acyl group for *o*-acylation. This redox-neutral method is compatible to a large number of directing arenes for the preparation of aliphatic ketones.

Experimental Section

General Procedure for Synthesis of 1-{2-(Benzo[*d*]thiazol-2-yl)phenyl}ethanone (1a) from 2-Phenylbenzo[*d*]thiazole (1)

To an oven-dried, 25-mL round-bottom flask were added 2-phenylbenzo[*d*]thiazole (**1**) (53 mg, 0.25 mmol), 3-acetyl-3-(*tert*-butylperoxy)-4-cyclohexylchroman-2-one (90 mg, 0.25 mmol), $Pd(TFA)_2$ (4 mg, 0.012 mmol), acetic acid (0.5 mL, 35 equiv.) and *p*-xylene (1.0 mL). Then the reaction mixture was refluxed in an oil bath preheated to 110 °C. After completion of the reaction (16 h), excess solvent was evaporated under reduced pressure. The crude product was extracted with ethyl acetate (3 × 10 mL) and the combined organic layer was washed carefully with saturated sodium bicarbonate solution (10 mL), dried over anhydrous sodium sulphate (Na_2SO_4), and evaporated under reduced pressure. The crude product so obtained was purified by silica gel column chromatography (hexane/ethylacetate, 10:0.3) to give 1-{2-(benzo[*d*]thiazol-2-yl)phenyl}ethanone (**1a**); yield: 38 mg (61%). The identity and purity of the product was confirmed by spectroscopic analysis.

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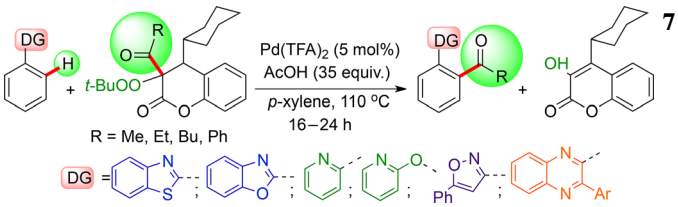

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