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Synthetic Methods

Hypervalent Iodine-Mediated Selective Oxidative Functionalization of (Thio)chromones with Alkanes

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Abstract: C–C bond formation is the most fundamental way for the chain propagation in organic molecules. This achievement through tandem oxidation of two different C–H bonds represents the state of the art in organic synthesis. Selective functionalization of the ubiquitous aliphatic C–H bonds offers an attractive option for this oxidative cross-coupling methodology. To develop such a methodology under mild and "metal-free" conditions remains challenging. Herein, we report hypervalent iodine-mediated selective oxidative functionalization of aliphatic C–H bonds of alkanes with chromones and (thio)chromones. A wide range of alkanes, both cyclic and acyclic, has been found to react selectively and predictably in good yields. The developed methodology is also the first report of a direct oxidative functionalization of the C-2 position of (thio)chromones with alkanes to access bioactive compounds.

The C–C bond represents the most essential and most abundant link in all organic molecules.[1] The quest for ever more efficient ways to construct C–C bonds represents a challenge for the synthetic chemists. One of the many ingenious ways to achieve this lays in cross-dehydrogenative coupling.[2] This methodology constructs carbon–carbon bonds through tandem oxidation of two C–H bonds present in the two coupling partners. The obvious benefit of this strategy is the smaller number of synthetic steps required to reach the target molecule, thereby making the synthesis highly efficient.[3] Aliphatic Csp^3–H bonds are omnipresent in organic molecules. Direct functionalization of aliphatic Csp^3–H bonds in a selective and predictable manner embodies a significant challenge in organic synthesis, because these bonds are of the least reactive bonds.[4] The apparent difference in reactivity of various types of aliphatic Csp^3–H bonds is not appreciable. Furthermore, during the functionalization of simple alkanes, weaker C–H bonds are engendered in the products. Therefore, products are more labile under reactions conditions and undergo over-functionalization. Despite these challenges, a lot of progress has been made in the area of oxidative functionalization of Csp^3–H bond to form carbon–heteroatom bonds.[5] Similarly, Csp^3–C bond formation through cross-dehydrogenative coupling has been achieved, but mostly by metal catalysis in combination with various oxidants.[6] Only a few mild and metal-free approaches for coupling with simple alkanes have been reported.[6d–e,7] Herein, we report a selective oxidative Csp^3–H bond functionalization of simple alkanes with chromones and (thio)-chromones under metal-free and ambient conditions.

As part of our continued interest in the area of C–H functionalization,[7,8] we have recently developed an iodine(III)-mediated[9] oxidative functionalization of simple alkanes with a variety of nitrogen heterocycles.[7] Based on the observations made during this study, we proposed that the alkyl radical generated under these conditions possess nucleophilic character. Nevertheless, the developed transformation is limited to electron-poor nitrogen-containing heterocycles. As a part of applying this methodology in the direct synthesis of bioactive compounds, we concentrated on utilizing chromone as the potential substrate. Chromone is an important structural motif present in many biologically important molecules.[10] Chromone alkaloids are abundant naturally occurring alkaloids forming the core of flavonoids. Derivatives of 2-alkylchromones have gained prominence as an extremely important class of inhibitors for a variety of biological targets (Figure 1).[11]

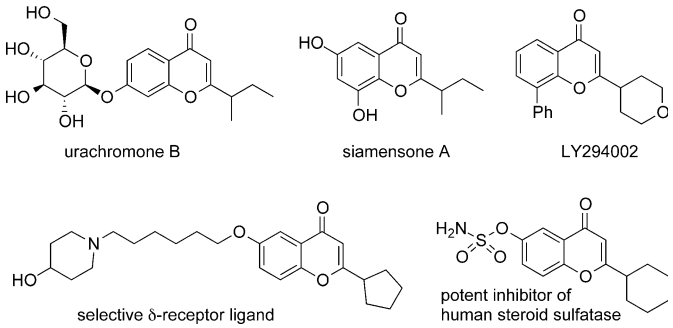

Figure 1. Representative structures of biologically relevant 2-alkylchromones.

Many approaches have been developed for the C-2 functionalization of chromones over the years. However, most of these efforts have been directed towards introducing aryl substituents to obtain flavones. Syntheses of 2-alkyl chromones in-

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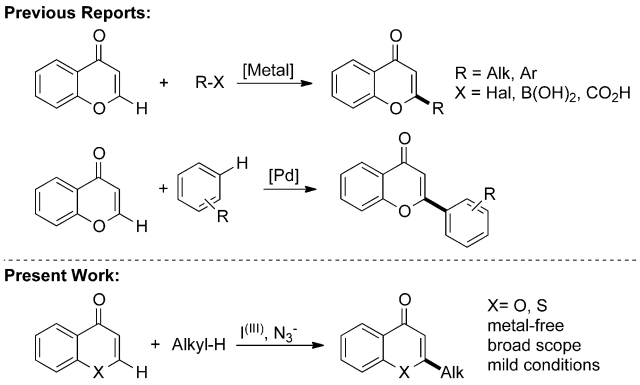
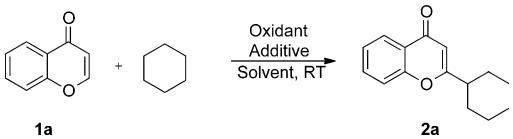
volve the usage of aliphatic aldehyde, which undergoes extensive self-condensation under the reaction conditions. Other multistep sequences have been developed to circumvent this problem and obtain C-2 alkyl chromones.[12] Recently, direct metal-catalyzed functionalization methods at the C2-position of chromones with pre-functionalized compounds have been developed.[13] For example, a silver-nitrate-catalyzed homolytic decarboxylative alkylation with aliphatic carboxylic acid has been reported.[13c] Nevertheless, this transformation led to the formation of mixtures of alkylated chromones and chromanones and has a limited scope. Very recently, an elegant regioselective palladium-catalyzed oxidative arylation of chromones through double C–H activation has been reported.[14] In this perspective, a dehydrogenative cross-coupling of chromones with alkanes would not only represent a significant advancement in the functionalization of alkanes, but also provide a very efficient access to biologically important 2-alkyl chromones (Scheme 1).



Scheme 1. Synthetic disconnection for oxidative C-2 functionalization of chromone derivatives.

Initially, the oxidative coupling of chromone **1a** with cyclohexane in the presence of two equivalents of $PhI(O_2CCF_3)_2$ and NaN_3 as the additive in CH_2Cl_2 at ambient temperature was tested. We were delighted to obtain the desired coupling product **2a** in 42% yield (Table 1, entry 1). When the amount of $PhI(O_2CCF_3)_2$ and NaN_3 was increased to three equivalents, a substantial improvement in the yield of product **2a** to 58% was observed (Table 1, entry 2). Further increase in the amount of oxidant and additive did not result in any improvement (Table 1, entry 3). Then we carried out a thorough screening of various solvents (Table 1, entries 4–7 and the Supporting Information). However, none of the screened solvents gave better results compared with CH_2Cl_2. Benzene could give the product **2a** in 16% yield (Table 1, entry 4). Other chlorinated solvents, such as 1,2-dichloroethane and $CHCl_3$, also gave the product **2a** in inferior yields of 42 and 33% respectively (Table 1, entries 5–6). The use polar solvents, such as EtOAc, MeOH, and CH_3CN, led to no reaction, and no product was observed (Table 1, entry 7, and the Supporting Information). Afterwards, various oxidants were screened. No product was detected in the presence of $PhI(OAc)_2$ (Table 1, entry 8). When compounds

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



1a 2a

Entry	Oxidant [equiv]	Additive [equiv]	Solvent	*t* [h]	Yield [%]
1	$PhI(O_2CCF_3)_2$ (2)	NaN_3 (2)	CH_2Cl_2	4	42
2	$PhI(O_2CCF_3)_2$ (3)	NaN_3 (3)	CH_2Cl_2	4	58
3	$PhI(O_2CCF_3)_2$ (4)	NaN_3 (4)	CH_2Cl_2	4	58
4	PhI(O2CCF3)2 (3)	NaN_3 (3)	PhH	16	16
5	$PhI(O_2CCF_3)_2$ (3)	NaN_3 (3)	$C_2H_4Cl_2$	16	42
6	$PhI(O_2CCF_3)_2$ (3)	NaN_3 (3)	$CHCl_3$	16	33
7	$PhI(O_2CCF_3)_2$ (3)	NaN_3 (3)	MeOH	16	n.d.
8	$PhI(OAc)_2$ (3)	NaN_3 (3)	CH_2Cl_2	24	n.d.
9	$C_6F_5I(O_2CCF3)_2$ (3)	NaN_3 (3)	CH_2Cl_2	16	<10
10	PhI(OH)OTs (3)	NaN_3 (3)	CH_2Cl_2	16	20
11[b]	$(BzO)_2$ (4)	–	$C_2H_4Cl_2$	16	50
12	$PhI(O_2CCF_3)_2$ (3)	$TMSN_3$ (3)	CH_2Cl_2	24	n.d.
13	$PhI(O_2CCF_3)_2$ (3)	tBu_4NN_3 (3)	CH_2Cl_2	24	n.d.
14[c]	$PhI(O_2CCF_3)_2$ (3)	NaN_3 (3)	CH_2Cl_2	24	31
15[d]	$PhI(O_2CCF3)_2$ (3)	NaN_3 (3)	CH_2Cl_2	8	61
16[e]	$PhI(O_2CCF_3)_2$ (4)	NaN_3 (4)	CH_2Cl_2	10	64
17[f]	$PhI(O_2CCF_3)_2$ (4)	NaN_3 (4)	CH_2Cl_2	10	72

[a] Reaction conditions: **1a** (0.14 mmol), cyclohexane (2.8 mmol), in solvent (1.0 mL) at RT. [b] The reaction was carried out in 1,2-dichloroethane at reflux. [c] The reaction was carried out at a concentration of 0.025 M. [d] Oxidant and additive were added in two portions of 1.5 equiv each. [e] Oxidant and additive were added in batches of 1.0 equiv in 1 h intervals. [f] Oxidant and additive were added in batches of 0.5 equiv in 1 h intervals. n.d. = not determined, $C_2H_4Cl_2$ = 1,2-dichloroethane.

$C_6F_5I(O_2CCF_3)_2$ and PhI(OH)OTs were used instead of $PhI(O_2CCF_3)_2$, the product **2a** was obtained in substantially lower yields of 10 and 20%, respectively (Table 1, entries 9-10). When benzoyl peroxide was used as the oxidant in 1,2-dichloroethane at reflux, 50% of **2a** was obtained without using any additives (Table 1, entry 11). Various peroxide oxidants, such as *tert*-butyl hydrogen peroxide (TBHP), di-*tert*-butyl peroxide (DTBP), and lauroyl peroxide did not initiate the radical reaction at all (see the Supporting Information for the details). Then, various azide sources, such as trimethylsilyl azide, *tert*-butylammonium azide, and phosphoryl azide were applied, but they all failed to give any product (Table 1, entries 12 and 13, and the Supporting Information). At this stage, with the best yield of 58%, we thought to further improve the efficiency of the reaction based on the use of the $PhI(O_2CCF_3)_2/NaN_3$ system. During the screening, we observed the formation of a side-product, which was identified as the product of double addition of cyclohexyl radical across the 2,3-double bond in chromone. We thought that the formation of this side-product could be suppressed by either dilution of the reaction medium or by addition of some hydrogen radical source. The radical reactions are known to be affected by the dilution of the reaction medium. When this reaction was carried out under much dilute condition of 0.025 M, the yield of the product plummeted to 31% (Table 1, entry 14).

A variety of hydrogen donors, such as Et_3SiH, $PhSiH_3$, 1,4-cyclohexadiene (CHD), and $NaBH_4$, were tested. Of these, CHD

gave the product in 42% yield, whereas $NaBH_4$ gave a comparable yield of 58% (see the Supporting Information for details). Nevertheless, we were unable to suppress the formation of the dialkylated product completely. We also observed in many cases that the conversion remained incomplete even after prolonged reaction time. To overcome this, we planned to add $PhI(O_2CCF_3)_2$ and NaN_3 in small batches. When a total of three equivalents of $PhI(O_2CCF_3)_2$ and NaN_3 was added in two batches of 1.5 equivalents each, slight increase in the yield to 61% was detected (Table 1, entry 15). Following this hint, the reaction was carried out by addition of one equivalent batch of the reagents, which increased the yield to 64%. In a 0.5 equivalent batch-mode addition, best yield of 72% was obtained (Table 1, entries 16–17). Syringe pump addition of $PhI(O_2CCF_3)_2$ over a period of 4 h resulted in reduced yield of 48%. Finally, we decided to use $PhI(O_2CCF_3)_2$ and NaN_3 in 0.5 equivalent batch-addition mode as the optimal reaction condition.

After obtaining the optimized reaction conditions, we explored the scope of this hypervalent iodine-mediated cross-dehydrogenative coupling of chromones and alkanes. First of all, the variation in the alkane part of the reaction was studied. The reaction was found to work well with a range of cycloalkanes of various ring sizes. Cyclopentane reacted to give the corresponding product **2b** in 58% yield (Figure 2). Similarly, cycloheptane and cyclo-octane also underwent smooth coupling to form products **2c** and **d** in 62 and 63% yields, respectively. An exclusive 3° site selectivity was observed for substituted cycloalkanes (Figure 2, compounds **2e** and **f**). The product of cross-coupling with methylcyclopentane was obtained in 60% yield. Reaction with 1,4-dimethylcyclohexane gave the corresponding product **2f** in 62% yield as *trans*/*cis* 5:1 isomer mixture. 1,1′-Dimethylcyclohexane also reacted well with 6-methylchromone to form the corresponding product **2g** as a mixture of positional isomers in the ratio of C2/C3/C4 1:12:5 and a combined yield of 57%. Only small amount of the regioisomer, corresponding to the functionalization at the sterically hindered C2 position, was observed. The regioisomer ratio at C-3 and C-4 positions correlates with the relative abundance of C–H bonds at the given position. For linear acyclic alkanes, exclusive 2° site selectivity was observed (Figure 2, products **2h–i**). The products were obtained as mixture of regioisomers at 2° sites. A notable selectivity of functionalization at C-2 position was observed. For example, in the case of *n*-hexane, the number of C–H bonds at C-2 and C-3 positions is equal. Furthermore, the difference in C–H bond dissociation energies for the process of *n*-hexane dissociation to 2-hexyl and 3-hexyl radicals is negligible (0.1–0.3 kcal mol^{-1}).[15] Therefore, the expected ratio of regioisomers at C2 and C3-positions is 1:1; however, obtained isomer ratio was 2.6:1. Applications of an acyclic branched alkane led to selective formation of the product with exclusive 3° site selectivity (Figure 2, product **2j**).

After studying the scope of alkanes in cross-coupling, we turned our attention towards substituted chromones. Various chromones containing electron-donating, as well as electron-withdrawing, substituents reacted selectively at C-2 position with cyclohexane to give the corresponding products in good yields (Figure 2, compounds **2k–q**). Chromones substituted

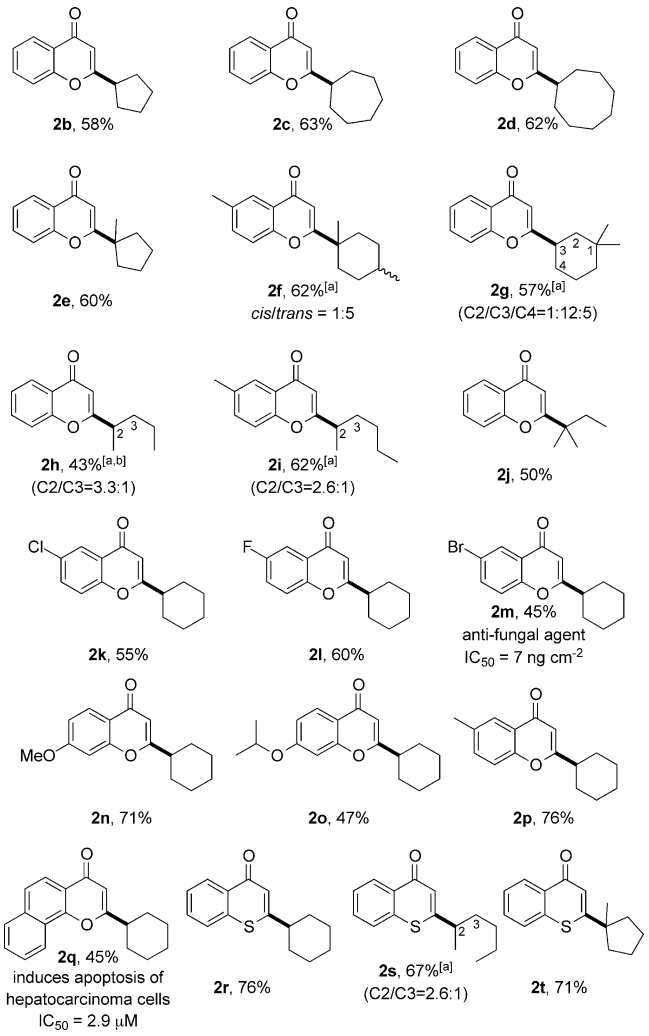
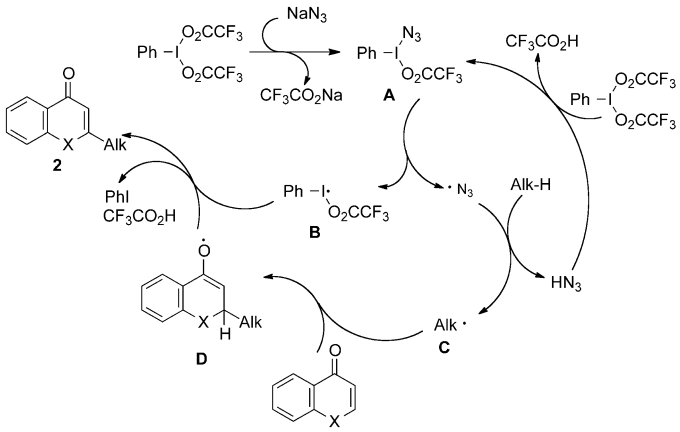


Figure 2. Scope of alkanes in cross-dehydrogenative coupling. Reaction conditions: chromone **1** (1 equiv), alkane (20 equiv), $PhI(O_2CCF_3)_2$ (4 equiv), and NaN_3 (4 equiv) in CH_2Cl_2 (1 mL) at RT. [a] Isomer ratio was determined based on ^1H NMR analysis. The structure of the major isomer is shown. [b] 34% of chromone was recovered.

with halogens at C6-position gave the corresponding products in 45–60% yield (compounds **2k–m**). Remarkably, 6-bromo-2-cyclohexylchromone (**2m**) has been found to possess extremely potent antifungal properties with an inhibitor concentration (IC_{50}) value of 7 ng cm^{-2}.[11d] 6-Methylchromone gave the cross-coupling product **2p** in good yield of 76%. Similarly, other electron-donating substituents, such as methoxy group, also reacted well to give the product **2n** in 71% yield. Even 6-isopropoxy-substituted chromone was tolerated well under the reaction conditions (**2o**). This is notable, because the tertiary C–H bond of isopropoxy group is weaker and more reactive under radical conditions compared with C–H bonds of cyclohexane. α-Naphthochromone underwent facile cross-coupling with cyclohexane to give product **2q** in an appreciable 45% yield. This compound has been known to induce apoptosis of hepatocarcinoma cells with an IC_{50} value of 2.9 μM.[11e] Moreover, highly conjugated aromatic systems, such as naphthochromone, are prone to oxidation under hypervalent iodine in-

duced oxidative conditions. To our delight, (thio)chromone reacts well under these conditions to form the cross-coupled product **2r** in good yield of 76%. Oxidation of the sulfur in the (thio)chromone to corresponding sulfone or sulfoxide was not observed, thus, indicating towards the chemoselective nature of the oxidative conditions. Similarly, when the (thio)chromone was cross-coupled with hexane, the corresponding product **2s** was obtained as a mixture of C2 and C3 regioisomers with 2.5:1 ratio. Methylcyclopentane reacted selectively at the 3° site to give product **2t** in 71% yield. Comparatively, the site selectivity of alkane for the dehydrogenative cross-coupling was found to be similar for both chromones and (thio)chromones. In both cases, desired products were formed selectively by functionalization of C2-position of (thio)chromone under mild reactions conditions. Furthermore, formation of by-products corresponding to alkanes' polyfunctionalization, homodimerization, and over-oxidation were not detected.

After exploring the scope of the cross-dehydrogenative coupling of chromones and alkanes, we turned our attention to the mechanism of the coupling. The formation of the products **2** was substantially suppressed in the presence of radical scavengers, such as (2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO). This fact clearly points to the involvement of radicals in the reaction. Based on this observation, a mechanistic rational has been proposed in Scheme 2. At first, $PhI(O_2CCF_3)_2$ reacts with NaN_3 through ligand exchange of trifluoroacetate for azide to form species **A**. This species undergoes thermolysis to generate an azide radical and an iodine-centered radical **B**. The azide radical abstracts a hydrogen atom from alkane to generate the alkyl radical **C** and hydrazoic acid. The alkyl radicals generated through this process possess nucleophilic character and attack the chromone at the most electrophilic C-2 position to generate radical **D**. This species was oxidized to the cross-coupled product **2**.



Scheme 2. Proposed mechanism for cross-coupling of (thio)chromones with simple alkanes.

In conclusion, we have developed a highly selective direct oxidative transition-metal-free protocol for cross-coupling of (thio)chromones and simple nonfunctionalized alkanes. This methodology provides a direct way to predictably functionalize unactivated Csp^3–H bonds with naturally abundant and biologically important chromones and (thio)chromones under ambient conditions. It also represents a significant advancement in the important and challenging area of metal-free Csp^3–Csp^2 cross-dehydrogenative coupling.

Experimental Section

General procedure for the synthesis of 2-alkyl(thio)chromones: To a dry screw capped vial chromone (0.14 mmol) was added and dissolved in 1 mL of CH_2Cl_2. To this solution 20 equiv of alkane was transferred followed by the addition of 0.5 equiv each of $PhI(O_2CCF_3)_2$ and NaN_3 under vigorous stirring at ambient temperature. The rest of the $PhI(O_2CCF_3)_2$ and NaN_3 (final amount used: 4 equiv) were added as batches of 0.5 equiv each with an interval of 1 h. The progress of the reaction was monitored by thin layer chromatography (ethyl acetate/petroleum ether mixture). Upon completion, the reaction mixture was quenched by the addition of triethylamine and the reaction mixture was directly subjected to silica-gel column chromatography using ethyl acetate/petroleum ether mixture as eluent to obtain the pure product.

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Keywords: C–H activation · chromones · iodine · metal-free conditions · oxidative coupling

[1] E. J. Corey, X. M. Cheng, *The Logic of Chemical Synthesis*, John Wiley & Sons, New York, **1989**.

[2] For reviews on cross-dehydrogenative coupling, see: a) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215–1292; b) M. Klussmann, D. Sureshkumar, *Synthesis* **2011**, 353–369; c) W.-J. Yoo, C.-J. Li, *Top. Curr. Chem.* **2009**, *292*, 281–302; d) J. A. Ashenhurst, *Chem. Soc. Rev.* **2010**, *39*, 540–548; e) C. J. Scheuermann, *Chem. Asian J.* **2010**, *5*, 436–451; f) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335–344; g) R. Rohlmann, O. G. Mancheno, *Synlett* **2013**, 6–10.

[3] For reviews on the ideal chemical synthesis, see: a) T. Gaich, P. S. Baran, *J. Org. Chem.* **2010**, *75*, 4657–4673; b) T. Newhouse, P. S. Baran, R. W. Hoffmann, *Chem. Soc. Rev.* **2009**, *38*, 3010–3021.

[4] For selected reviews on Csp^3–H bond functionalization: a) M. C. White, *Science* **2012**, *335*, 807–809; b) J. L. Roizen, M. E. Harvey, J. Du Bois, *Acc. Chem. Res.* **2012**, *45*, 911–922; c) M. Uyanik, K. Ishihara, *ChemCatChem* **2012**, *4*, 177–185; d) T. Brückl, R. D. Baxter, Y. Ishihara, P. S. Baran, *Acc. Chem. Res.* **2012**, *45*, 826–839; e) S. Y. Zhang, F. M. Zhang, Y. Q. Tu, *Chem. Soc. Rev.* **2011**, *40*, 1937–1949; f) J. Wencel-Delord, T. Droge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740–4761; g) T. Newhouse, P. S. Baran, *Angew. Chem.* **2011**, *123*, 3422–3435; *Angew. Chem. Int. Ed.* **2011**, *50*, 3362–3374; h) L. McMurray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev.* **2011**, *40*, 1885–1898; i) C. Liu, H. Zhang, W. Shi, A. W. Lei, *Chem. Rev.* **2011**, *111*, 1780–1824; j) Y. Kuninobu, K. Takai, *Chem. Rev.* **2011**, *111*, 1938–1953; k) R. Samanta, K. Matcha, A. P. Antonchick, *Eur. J. Org. Chem.* **2013**, 5769–5804.

[5] Recent examples of Csp^3–N bond formation: a) A. J. Neel, J. P. Hehn, P. F. Tripet, F. D. Toste, *J. Am. Chem. Soc.* **2013**, *135*, 14044–14047; b) S. M. Paradine, M. C. White, *J. Am. Chem. Soc.* **2012**, *134*, 2036–2039; c) A. Nörder, S. A. Warren, E. Herdtweck, S. M. Huber, T. Bach, *J. Am. Chem. Soc.* **2012**, *134*, 13524–13531; d) Z. K. Ni, Q. Zhang, T. Xiong, Y. Y. Zheng, Y. Li, H. W. Zhang, J. P. Zhang, Q. Liu, *Angew. Chem.* **2012**, *124*, 1270–1273; *Angew. Chem. Int. Ed.* **2012**, *51*, 1244–1247; e) E. T. Nadres, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 7–10; f) Q. Michaudel, D. Thevenet, P. S. Baran, *J. Am. Chem. Soc.* **2012**, *134*, 2547–2550; g) G. He,

Y. S. Zhao, S. Y. Zhang, C. X. Lu, G. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 3 – 6; Recent examples of Csp^3–O bond formation h) P. E. Gormisky, M. C. White, *J. Am. Chem. Soc.* **2013**, *135*, 14052 – 14055; i) S. Y. Zhang, G. He, Y. S. Zhao, K. Wright, W. A. Nack, G. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 7313 – 7316; j) E. M. Simmons, J. F. Hartwig, *Nature* **2012**, *483*, 70 – 73; k) E. McNeill, J. Du Bois, *Chem. Sci.* **2012**, *3*, 1810 – 1813; l) M. A. Bigi, S. A. Reed, M. C. White, *J. Am. Chem. Soc.* **2012**, *134*, 9721 – 9726.

[6] Recent examples for cross-dehydrogenative coupling for the formation of Csp^3–C bond: a) S. Guin, S. K. Rout, A. Banerjee, S. Nandi, B. K. Patel, *Org. Lett.* **2012**, *14*, 5294 – 5297; b) Z. Xie, Y. Cai, H. Hu, C. Lin, J. Jiang, Z. Chen, L. Wang, Y. Pan, *Org. Lett.* **2013**, *15*, 4600 – 4603; c) X.-F. Huang, Z.-Q. Zhu, Z.-Z. Huang, *Tetrahedron* **2013**, *69*, 8579 – 8582; for selected examples on metal-free Csp^3–C bond formation with non-activated alkanes, see: d) G. Deng, K. Ueda, S. Yanagisawa, K. Itami, C.-J. Li, *Chem. Eur. J.* **2009**, *15*, 333 – 337; e) R. Xia, H.-Y. Niu, G.-R. Qu, H.-M. Guo, *Org. Lett.* **2012**, *14*, 5546 – 5549.

[7] A. P. Antonchick, L. Burgmann, *Angew. Chem.* **2013**, *52*, 3267 – 3271; *Angew. Chem. Int. Ed.* **2013**, *125*, 3349 – 3353.

[8] a) R. Samanta, J. Lategahn, A. P. Antonchick, *Chem. Commun.* **2012**, *48*, 3194 – 3196; b) R. Samanta, K. Kulikov, C. Strohmann, A. P. Antonchick, *Synthesis* **2012**, 2325 – 2332; c) R. Samanta, J. O. Bauer, C. Strohmann, A. P. Antonchick, *Org. Lett.* **2012**, *14*, 5518 – 5521; d) A. P. Antonchick, R. Samanta, K. Kulikov, J. Lategahn, *Angew. Chem.* **2011**, *123*, 8764 – 8767; *Angew. Chem. Int. Ed.* **2011**, *50*, 8605 – 8608; e) K. Matcha, A. P. Antonchick, *Angew. Chem.* **2013**, *125*, 2136 – 2140; *Angew. Chem. Int. Ed.* **2013**, *52*, 2082 – 2086; f) R. Samanta, A. P. Antonchick, *Synlett* **2012**, 809 – 813; g) K. Matcha, R. Narayan, A. P. Antonchick, *Angew. Chem.* **2013**, *52*, 7985 – 7989; *Angew. Chem. Int. Ed.* **2013**, *125*, 8143 – 8147; h) R. Samanta, R. Narayan, A. P. Antonchick, *Org. Lett.* **2012**, *14*, 6108 – 6111; i) Z. Q. Song, R. Samanta, A. P. Antonchick, *Org. Lett.* **2013**, *15*, 5662 – 5665; j) R. Samanta, A. P. Antonchick, *Angew. Chem.* **2011**, *123*, 5323 – 5326; *Angew. Chem. Int. Ed.* **2011**, *50*, 5217 – 5220.

[9] For reviews on the chemistry of iodine(III), see: a) M. S. Yusubov, V. V. Zhdankin, *Curr. Org. Synth.* **2012**, *9*, 247 – 272; b) J. L. F. Silva Jr., B. Olofsson, *Nat. Prod. Rep.* **2011**, *28*, 1722 – 1754; c) E. A. Merritt, B. Olofsson, *Synthesis* **2011**, 517 – 538; d) J. P. Brand, D. F. Gonzalez, S. Nicolai, J. Waser, *Chem. Commun.* **2011**, *47*, 102 – 115; e) V. V. Zhdankin, *ARKIVOC (Gainesville, FL, U.S.)* **2009**, 1 – 62; f) M. Uyanik, K. Ishihara, *Chem. Commun.* **2009**, 2086 – 2099; g) T. Dohi, M. Ito, N. Yamaoka, K. Morimoto, H. Fujioka, Y. Kita, *Tetrahedron* **2009**, *65*, 10797 – 10815; h) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299 – 5358; i) S. Quideau, L. Pouysegu, D. Deffieux, *Synlett* **2008**, 467 – 495; j) M. Ochiai, *Chem. Rec.* **2007**, *7*, 12 – 23; k) M. A. Ciufolini, N. A. Braun, S. Canesi, M. Ousmer, J. Chang, D. Chai, *Synthesis* **2007**, 3759 – 3772; l) T. Wirth, *Angew. Chem.* **2005**, *117*, 3722 – 3731; *Angew. Chem. Int. Ed.* **2005**, *44*, 3656 – 3665.

[10] a) S. Khadem, R. J. Marles, *Molecules* **2011**, *17*, 191 – 206; b) J. S. Yoon, M. K. Lee, S. H. Sung, Y. C. Kim, *J. Nat. Prod.* **2006**, *69*, 290 – 291; c) J. López-Martín, E. M. Anam, H. Boira, M. J. Sanz, M. A. Blazquez, *Chem. Pharm. Bull.* **2002**, *50*, 1613 – 1615; d) K. M. Biswas, H. Mallik, *Phytochemistry* **1986**, *25*, 1727 – 1730; e) C. A. Engelhart, C. C. Aldrich, *J. Org. Chem.* **2013**, *78*, 7470 – 7481; f) R. G. Naik, S. L. Kattige, S. V. Bhat, B. Alreja, N. J. de Souza, R. H. Rupp, *Tetrahedron* **1988**, *44*, 2081 – 2086.

[11] a) P. Nussbaumer, A. P. Winiski, A. Billich, *J. Med. Chem.* **2003**, *46*, 5091 – 5094; b) P. Nussbaumer, P. Lehr, A. Billich, *J. Med. Chem.* **2002**, *45*, 4310 – 4320; c) F. Rodríguez-Ramos, A. Navarrete, M. González-Andrade, C. Alarcón, A. Aguilera-Cruz, A. Reyes-Ramírez, *Bioorg. Chem.* **2013**, *50*, 17 – 25; d) S. B. Abdel Ghani, P. J. Mugisha, J. C. Wilcox, E. A. M. Gado, E. O. Medu, A. J. Lamb, R. C. D. Brown, *Synth. Commun.* **2013**, *43*, 1549 – 1556; e) H. Liu, A. Dong, C. Gao, C. Tan, Z. Xie, X. Zu, L. Qu, Y. Jiang, *Bioorg. Med. Chem.* **2010**, *18*, 6322 – 6328; f) G. A. Morales, J. R. Garlich, J. Su, X. Peng, J. Newblom, K. Weber, D. L. Durden, *J. Med. Chem.* **2013**, *56*, 1922 – 1939; g) X. Q. Chen, Y. Li, X. Cheng, K. Wang, J. He, Z. H. Pan, M. M. Li, L. Y. Peng, G. Xu, Q. S. Zhao, *Chem. Biodiversity* **2010**, *7*, 196 – 204; h) S. Laphookhieo, W. Maneerat, R. Kiattansakul, *Can. J. Chem.* **2006**, *84*, 1546 – 1549; i) R. H. Erickson, K. J. Natalie, W. Bock, Z. J. Lu, F. Farzin, R. G. Sherrill, D. J. Meloni, R. J. Patch, W. J. Rzesotarski, J. Clifton, M. J. Pontecorvo, M. A. Bailey, K. Naper, W. Karbon, *J. Med. Chem.* **1992**, *35*, 1526 – 1535.

[12] a) M. Fridén-Saxin, N. Pemberton, K. S. Andersson, C. Dyrager, A. Friberg, M. Grøtli, K. Luthman, *J. Org. Chem.* **2009**, *74*, 2755 – 2759; b) D. Pflieger, B. Muckensturm, *Tetrahedron Lett.* **1990**, *31*, 2299 – 2300; c) M. Yoshida, Y. Fujino, K. Saito, T. Doi, *Tetrahedron* **2011**, *67*, 9993 – 9997; d) J. Liu, M. Liu, Y. Yue, N. Zhang, Y. Zhang, K. Zhuo, *Tetrahedron Lett.* **2013**, *54*, 1802 – 1807; e) Q. Yang, H. Alper, *J. Org. Chem.* **2010**, *75*, 948 – 950; f) E. Awuah, A. Capretta, *Org. Lett.* **2009**, *11*, 3210 – 3213; g) B. Liang, M. Huang, Z. You, Z. Xiong, K. Lu, R. Fathi, J. Chen, Z. Yang, *J. Org. Chem.* **2005**, *70*, 6097 – 6100; h) L. Xue, L. Shi, Y. Han, C. Xia, H. V. Huynh, F. Li, *Dalton Trans.* **2011**, *40*, 7632 – 7638; i) D.-W. Chuang, M. El-Shazly, B. Balaji, Y.-M. Chung, F.-R. Chang, Y.-C. Wu, *Eur. J. Org. Chem.* **2012**, *2012*, 4533 – 4540; j) S. Zhang, C. Wan, Q. Wang, B. Zhang, L. Gao, Z. Zha, Z. Wang, *Eur. J. Org. Chem.* **2013**, *2013*, 2080 – 2083.

[13] a) L. Klier, T. Bresser, T. A. Nigst, K. Karaghiosoff, P. Knochel, *J. Am. Chem. Soc.* **2012**, *134*, 13584 – 13587; b) M. Khoobi, M. Alipour, S. Zarei, F. Jafarpour, A. Shafiee, *Chem. Commun.* **2012**, *48*, 2985 – 2987; c) J. F. J. Engbersen, A. Koudijs, H. C. van der Plas, *J. Heterocycl. Chem.* **1982**, *19*, 1281 – 1283.

[14] J. N. Kim, K. H. Kim, S. H. Kim, H. S. Lee, *Tetrahedron Lett.* **2012**, *53*, 2761 – 2764.

[15] J. Zheng, T. Yu, D. G. Truhlar, *Phys. Chem. Chem. Phys.* **2011**, *13*, 19318 – 19324.

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Synthetic Methods

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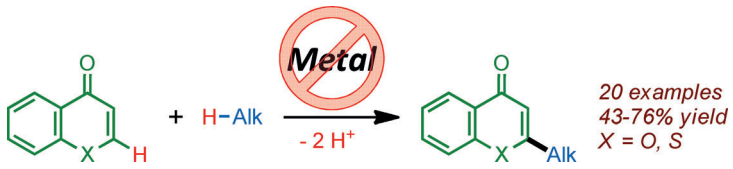
Hypervalent Iodine-Mediated Selective Oxidative Functionalization of (Thio)chromones with Alkanes



Hypervalent iodine: An efficient I^{III}-mediated selective oxidative functionalization of alkanes with chromones and (thio)chromones has been developed. The developed methodology provides a direct access to the 2-alkyl chromones under metal-free and ambient conditions. Both cyclic and acyclic alkanes can be selectively functionalized (see scheme).