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Expeditious Synthesis of Benzopyrans via Lewis Acid-Catalyzed C−H Functionalization: Remarkable Enhancement of Reactivity by an *Ortho* Substituent

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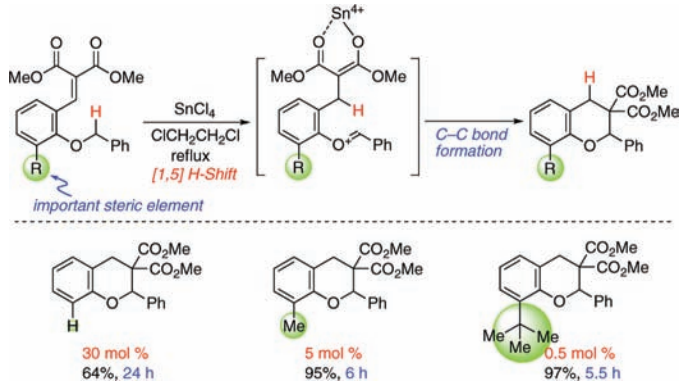
ABSTRACT



An expeditious construction of a benzopyran skeleton via Lewis acid-catalyzed C−H functionalization was achieved. In this process, a [1,5] hydride shift and 6-*endo* cyclization successively occurred to give benzopyrans. The presence of substituents ortho to the alkoxy group significantly enhanced the reactivity, affording the desired compounds in excellent chemical yields with short reaction times.

The development of methods for the direct functionalization of relatively unreactive C−H bonds has now become a major topic in synthetic organic chemistry.[1] Such methods have enabled the formation of C−C and/or C−Y bonds (Y = O, N, etc.) without prefunctionalization to C−X bonds (X = halogens, OSO_2CF_3, etc.).

Recently, the sp^3 C−H functionalization via internal redox processes has attracted much attention due to its unique features, as outlined in Scheme 1.[2] First, the C−H bond α to the amine nitrogen of **1** was cleaved via a [1,5] hydride shift to give iminium intermediate **A**. Subsequent 6-endo cyclization afforded tetrahydroquinoline derivative **2**. Although the C−H functionalization was mostly promoted by a transition metal catalyst, the

(1) For recent reviews on C−H activation, see: (a) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (b) Davies, H. M. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6422. (c) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (d) Bergman, R. G. *Nature* **2007**, *446*, 391. (e) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174.

(2) For selected recent references, see: (a) Pastine, S. J.; McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 12180. (b) Pastine, S. J.; Sames, D. *Org. Lett.* **2005**, *7*, 5429. (c) Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1683. (d) Barluenga, J.; Fananás-Mastral, M.; Aznar, F.; Valdés, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 6594. (e) McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 402. (f) Shikanai, D.; Murase, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2009**, *131*, 3166. (g) Murarka, S.; Deb, I.; Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 13226. (h) Vadola, P. A.; Sames, D. *J. Am. Chem. Soc.* **2009**, *131*, 16525.

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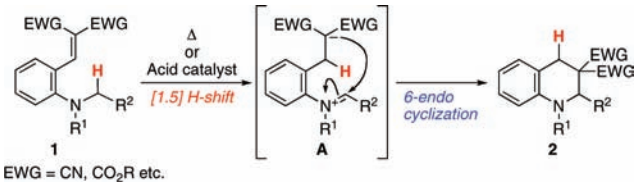
Scheme 1. C−H Functionalization via Internal Redox Process

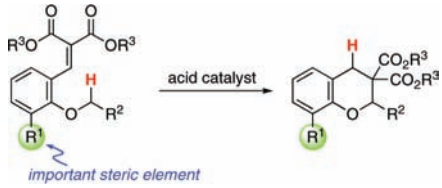


internal redox processes typically proceeded under thermal conditions or, in some cases, under Brønsted or Lewis acid catalysis.[3,4]

As part of our ongoing effort to develop new catalytic transformations, we found that the imine derivative was also viable for the internal redox processes.[5] Seidel and co-workers recently reported the $Gd(OTf)_3$-facilitated [1,5] hydride shift without heating (room temperature), affording tetrahydroisoquinoline derivatives.[6] A number of related reactions with nitrogen-containing substrates have been reported. Although Sames and co-workers have extensively studied the oxygen version,[2a,b,e,h] the formation of benzopyran derivatives remains to be investigated.[7]

We report herein a highly efficient method for the construction of a benzopyran skeleton via Lewis acid catalyzed C−H bond functionalization (Scheme 2). It is noted that the presence

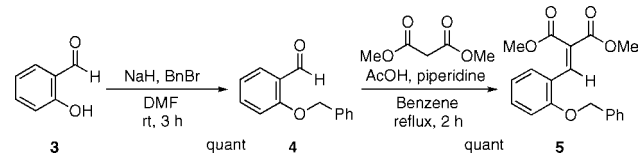
Scheme 2. Expeditious Construction of Benzopyran Skeleton



of a substituent ortho to the alkoxy group had a remarkable influence on the reactivity, affording the desired benzopyrans in excellent chemical yields with short reaction times.

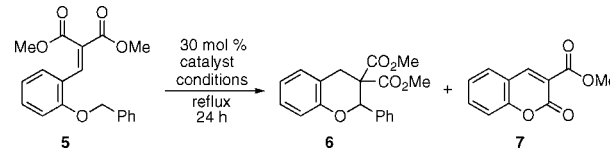
According to our previous report,[5] benzyloxy benzylidene malonate **5** was chosen as a suitable substrate for the proposed reaction, which was easily synthesized from salicylaldehyde (**3**). Benzylation of the hydroxy group of **3** followed by Knoevenagel condensation with dimethyl malonate gave **5** in quantitative yield (Scheme 3).

Scheme 3. Preparation of Benzylidene Malonate **5**



Having the requisite substrate, the planned cyclization was attempted: a solution of **5** in $ClCH_2CH_2Cl$ was exposed to several acids (Table 1). On treatment of **5** with $TsOH{\cdot}H_2O$,

Table 1. Examination of Reaction Conditions[a]



			yield (%)	
entry	catalyst	solvent	**6**[b]	**7**[c]
1	$TsOH{\cdot}H_2O$	$ClCH_2CH_2Cl$		85
2	TfOH	$ClCH_2CH_2Cl$		83
3	$MgBr_2$	$ClCH_2CH_2Cl$	− (80)	
4	$Yb(OTf)_3$	$ClCH_2CH_2Cl$	− (95)	
5	$Sc(OTf)_3$	$ClCH_2CH_2Cl$	69[c]	9
6	$TiCl_4$	$ClCH_2CH_2Cl$	− (61)	6
7	$SnCl_4$	$ClCH_2CH_2Cl$	64[c]	18
8	$SnCl_4$	CH_3CN	− (80)	7
9[d]	$SnCl_4$	toluene	15 (50)	31
10	$SnCl_4$	benzene	35	61
11	$SnCl_4$	cyclohexane	2 (85)	8

[a] Unless otherwise noted, all reactions were performed with 0.2 mmol of **5** and 30 mol % of catalyst in solvent (2.0 mL) at refluxing temperature. [b] ^1H NMR yield. Recovery of **5** is indicated in parentheses. [c] Isolated yield. [d] At 90 °C.

starting material **5** was almost completely consumed after 24 h (entry 1). Disappointingly, the resulting product was not the desired product **6** but coumarin **7**, which was produced by debenzylation followed by internal cyclization. TfOH also gave

(3) These types of reactions have been classified under the term *tert*-amino effect. For reviews, see: (a) Meth-Cohn, O.; Suschitzky, H. *Adv. Heterocycl. Chem.* **1972**, *14*, 211. (b) Verboom, W.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 311. (c) Meth-Cohn, O. *Adv. Heterocycl. Chem.* **1996**, *65*, 1. (d) Quintela, J. M. *Recent Res. Dev. Org. Chem.* **2003**, *7*, 259. (e) Matyus, P.; Elias, O.; Tapolcsanyi, P.; Polonka-Balint, A.; Halasz-Dajka, B. *Synthesis* **2006**, 2625.

(4) (a) Verboom, W.; Reinhoudt, D. N.; Visser, R.; Harkema, S. *J. Org. Chem.* **1984**, *49*, 269. (b) Nijhuis, W. H. N.; Verboom, W.; Reinhoudt, D. N.; Harkema, S. *J. Am. Chem. Soc.* **1987**, *109*, 3136. (c) Nijhuis, W. H. N.; Verboom, W.; Reinhoudt, D. N. *Synthesis* **1987**, 641. (d) Nijhuis, W. H. N.; Verboom, W.; Abu El-Fadl, A.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1989**, *54*, 199. (e) Nijhuis, W. H. N.; Verboom, W.; Abu El-Fadl, A.; Van Hummel, G. J.; Reinhoudt, D. N. *J. Org. Chem.* **1989**, *54*, 209. (f) De Boeck, B.; Jiang, S.; Janousek, Z.; Viehe, H. G. *Tetrahedron* **1994**, *50*, 7075. (g) De Boeck, B.; Janousek, Z.; Viehe, H. G. *Tetrahedron* **1995**, *51*, 13239. (h) Ojea, V.; Muinelo, I.; Quintela, J. M. *Tetrahedron* **1998**, *54*, 927. (i) Kaval, N.; Halasz-Dajka, B.; Vo-Thanh, G.; Dehaen, W.; Van der Eycken, J.; Matyus, P.; Loupy, A.; Van der Eycken, E. *Tetrahedron* **2005**, *61*, 9052. (j) Zhang, C.; Kanta De, C.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416. (k) Ruble, J. C.; Hurd, A. R.; Johnson, T. A.; Sherry, D. A.; Barbachyn, M. R.; Toogood, P. L.; Bundy, G. L.; Graber, D. R.; Kamilar, G. M. *J. Am. Chem. Soc.* **2009**, *131*, 3991. (l) Tobisu, M.; Nakai, H.; Chatani, N. *J. Org. Chem.* **2009**, *74*, 5471.

(5) Mori, K.; Ohshima, Y.; Ehara, K.; Akiyama, T. *Chem. Lett.* **2009**, *38*, 524. Seidel reported a similar redox process promoted by TfOH: Zhang, C.; Murarka, S.; Seidel, D. *J. Org. Chem.* **2009**, *74*, 419.

(6) Murarka, S.; Zhang, C.; Konieczynska, M. D.; Seidel, D. *Org. Lett.* **2009**, *11*, 129.

(7) During the preparation of our manuscript, Sames reported a similar redox process promoted by $Sc(OTf)_3$: McQuaid, K. M.; Long, J. Z.; Sames, D. *Org. Lett.* **2009**, *11*, 2972.

7 in 83% yield (entry 2). Both $MgBr_2$ and $Yb(OTf)_3$ were insufficient catalysts, and the starting material was recovered (entries 3 and 4). Gratifyingly, $Sc(OTf)_3$ furnished the desired product in 69% yield. Further screening of the catalysts revealed that $SnCl_4$ was the most effective from both practical and economic viewpoints, giving **6** in good yield (64%). Another solvent system was also examined (entries 8−11), suggesting that nonpolar solvents were suitable for this reaction, and $ClCH_2CH_2Cl$ was the solvent of choice.

Figure 1 illustrates the substrate scope of this reaction. At first, several substrates bearing a methyl group at various

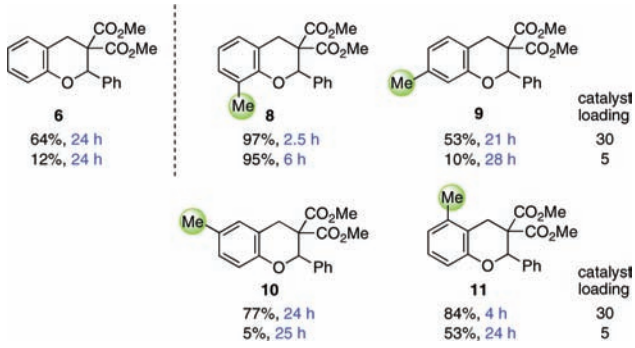


Figure 1. Substituent effect of the methyl group.

positions of the aromatic ring were examined, which offered quite interesting results: the position of the methyl group played a critical role on the reactivity. In all cases, the desired products were obtained. Interestingly, in the case of substrates with a methyl group at the position ortho to the alkoxy group or the benzylidene moiety, a dramatic enhancement of the reactivity compared with nonsubstituted substrate **5** was observed, affording **8** and **11** in excellent yields with short reaction times (97%, 2.5 h and 84%, 4 h, respectively). In particular, **8** was obtained in excellent yield with a short reaction time (95%, 6 h) even when the reaction was performed with 5 mol % catalyst loading.

This remarkable enhancement of the reactivity by the methyl group ortho to the alkoxy group could be well rationalized by taking two factors into consideration: (1) the conformational behavior of the benzyloxy group and (2) the "buttressing effect"[8] (Figure 2). To promote the desired [1,5]

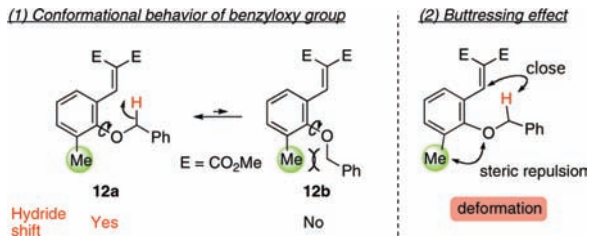
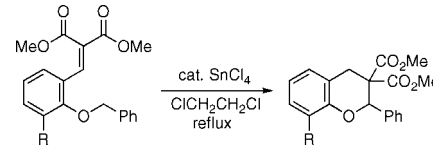


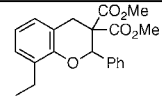
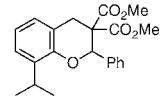
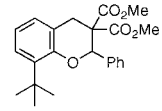
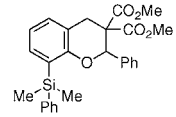
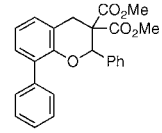
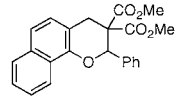
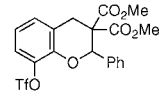
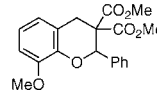
Figure 2. Rationalization for the enhancement of reactivity by ortho substituents.

hydride shift, conformer **a**, whose benzylic hydrogens were located close to the electrophilic carbon of malonate C=C bond, should be taken. In the case of **12** having an *o*-methyl group, the conformational equilibrium largely shifted to desired conformer **12a** because of the severe steric repulsion between the methyl group and the benzyloxy group. Furthermore, the "buttressing effect" between the methyl group and the benzyloxy group made the hydrogens on the benzyl group much more closer to the benzylidene electrophilic carbon. As a result of the cooperative effect of these two factors, the reactivity of **12** improved significantly, and both catalyst loading and reaction time could be dramatically reduced.[9,10]

To gain further insight into the "*ortho substituent effect*," a range of substrates were examined under the optimal conditions (Table 2). First, the steric effect was investigated.

Table 2. Examination of Reactivity Alteration by Ortho Substituents



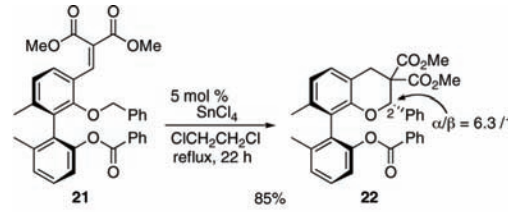
entry	product		catalyst loading (mol %)	time (h)	yield (%)[b]
1		**13**	5	3	99
2		**14**	5	2	97
3		**15**	5	<0.5	99
			0.5	5.5	97
4		**16**	5	1	92
5		**17**	5	8.5	91
6		**18**	5	24	97
7		**19**	30	9	53
			5	24	5
8		**20**	30	24	–
			5	24	trace

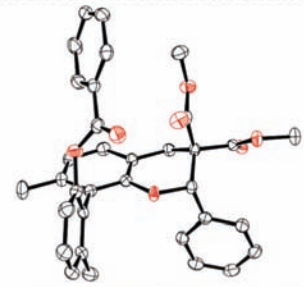
[a] Unless otherwise noted, all reactions were performed with 0.2 mmol of malonate and a catalytic amount of $SnCl_4$ in $ClCH_2CH_2Cl$ (2.0 mL) at refluxing temperature. [b] Isolated yield.

The results suggested that increasing the size of the ortho substituents shortened the reaction time (entries 1−3). In the case of the ethyl-substituted substrate, the reaction was completed in 3 h (99%, entry 1). Isopropyl-substituted product **14** was obtained in excellent yield within 2 h (97%, entry 2). It is noted that the introduction of a bulky *t*-Bu group significantly improved the reactivity, and **15** was obtained in quantitative yield within less than 0.5 h by means of 5 mol % catalyst loading. The catalyst loading could be reduced to as low as 0.5 mol % without sacrificing the chemical yield (97%, 5.5 h, entry 3).[11] Excellent chemical yield with a short reaction time was achieved in dimethylphenylsilyl-substituted product **16** (92%, 1 h, entry 4). Biphenyl- and naphthyl-type products (**17** and **18**) were also obtained in excellent yields, although in those cases, prolonged reaction times were required, presumably due to the less steric bulkiness of the substituents (entries 5 and 6). The survey of the electronic effect revealed that the steric effect was the most important factor to enhance reactivity (entries 7 and 8). Triflate **19** was obtained in only moderate yield even with 30 mol % catalyst loading (53%, entry 7). The methoxy-substituted substrate gave many byproducts, and desired product **20** could not be obtained (entry 8).

To demonstrate the utility of this method, the diastereoselective reaction was also conducted: a malonate with a tetrasubstituted biphenyl backbone **21** was exposed to the optimized conditions (Scheme 4). Gratifyingly, desired product **22** was obtained in excellent yield with the α isomer being predominant (85%, $\alpha/\beta = 6.3/1$).[12] This result suggested that the internal chiral information (axial chirality in the biphenyl core) had a pronounced influence on the stereochemistry of the newly formed stereogenic center.

Scheme 4. Diastereoselective Reaction





X-ray structure of **22α**. Hydrogen atoms are omitted for clarity.

In summary, an expeditious construction of a benzopyran framework via Lewis acid-catalyzed C−H bond functionalization was achieved. The presence of a bulky substituent at the position ortho to the alkoxy group played a critical role on the reactivity; i.e., both reaction time and catalyst loading could be dramatically reduced. Furthermore, the newly formed stereogenic center could be partially controlled by internal chiral information. Further investigation of its application to natural product synthesis is underway in our laboratory.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental procedures, analytical and spectroscopic data for new compounds, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL100316K

(8) *Stereochemistry of Organic Compounds*; Eliel, E. D., Wilen, S. H., Eds.; Wiley-Interscience: Markham, ON, 1994; Chapter 14, p 1455.

(9) The reactivity improvement of **11** was also ascribed to the "buttressing effect" between the methyl group and the benzylidene moiety, which forced the benzylidene moiety to be positioned close to the benzyloxy group.

(10) The electronic stabilization of the oxonium cation generated after the [1,5] hydride shift by an *o*-methyl group had a minimal influence on the enhancement of the reactivity. This supposition was recognized by comparing the results of **9** and **10** (Figure 1). The chemical yield of **10** with a methyl group para to the alkoxy group, whose position was suitable for the stabilization of the oxonium cation compared to the meta position, was higher than that of **9** (with 30 mol % of $SnCl_4$).

(11) The order of reactivity of these substrates was in good agreement with that of flipping energy in cyclohexane, namely, "*A* value". See: *Stereochemistry of Organic Compounds*, Eliel, E. D.; Wilen, S. H. Wiley-Interscience: Markham, ON, 1994; Chapter 11, p 695.

(12) The diastereomeric ratio was determined by comparing the integration value of each C-2 hydrogen in ^{1}H NMR ($CDCl_3$). The relative stereochemistry of the major isomer was unambiguously established by single crystal X-ray analysis. CCDC-763440 contains the supplementary crystallographic data of **22α**. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request.