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# Rhodium-catalyzed cyclopropanations of 2-aryl-2*H*-chromenes with dialkyl malonate esters. A comparison of α-diazo derivatives and phenyliodonium ylides

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Dedicated to my good friend and mentor Professor Philip J. Parsons on the occasion of his 60th birthday

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ABSTRACT

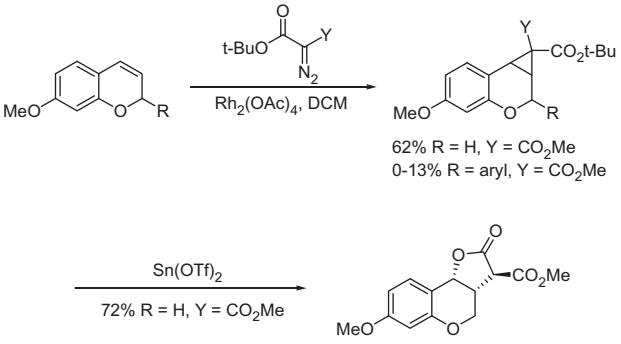
Rhodium-catalyzed reactions of 2-aryl-substituted 2*H*-chromenes with α-diazo esters prepared from dimethyl and *tert*-butyl methyl malonates were investigated, and the results were compared with reactions carried out with phenyliodonium ylides prepared from the same esters. The phenyliodonium ylide prepared from dimethyl malonate was found to give superior yields of cyclopropane products compared to the corresponding α-diazo equivalent. However, this result was reversed with *tert*-butyl methyl malonate when $Rh_2$(S-TBSP)$_4$ was used to decompose the diazo compound. All reactions gave 1,1-cyclopropane diesters as single diastereomers.



Aryl-substituted benzodihydropyrans or chromans are associated with a broad range of biological activities, including anticancer,[1] antibacterial,[2] antifungal,[3] anti-inflammatory,[3] and anti-malarial properties.[4] A number of these compounds, such as the myristinins,[3,5] licoricidin,[2] and licorisoflavan,[2] are naturally-occurring. However, many promising lead compounds have also been identified through analogue synthesis,[1] which places a premium on new synthetic methods that offer access to novel chroman-based structures.

Because the alkene moiety of 2*H*-chromenes has been shown to be highly susceptible to functionalization with electrophilic reagents and dipolarophiles,[6] the derivatization of easily-accessible 2-aryl-2*H*-chromenes offers an obvious approach to structures of interest.[7] In that context, we recently reported a two-step approach to tetrahydro-2*H*-furochromenones with complete diastereo- and regioselectivity. This entails reaction with α-substituted α-diazo *tert*-butyl acetates under rhodium catalysis to form donor–acceptor cyclopropane derivatives which rearranged upon treatment with $Sn(OTf)_2$ (Scheme 1).[8] We found that the use of more standard methods for lactonizing alkenes, which typically require the use of oxidizing conditions,[9] caused unwanted side reactions such as aromatization of the pyran ring.[10] However, one limitation of our method was the low reactivity of the 2*H*-chromene when it was substituted at the 2-position by an aryl substituent. In these cases, mostly starting material was recovered and very little cyclopropane product was isolated.

Iodonium ylides have offered a convenient and safer alternative to diazo compounds for alkene cyclopropanations. They are more reactive than their diazo equivalents, and often require smaller catalyst loadings.[11] However, they are also known to be less stable and quickly degrade.[11,12] The in situ generation of these reagents has been used to circumvent this problem, but this can result in




**Scheme 1.** General route to tetrahydro-2*H*-furochromenones.

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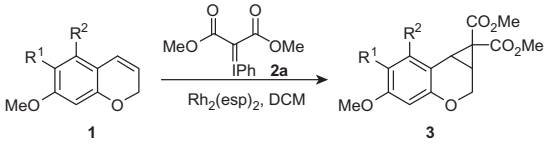
**Table 1**
Reactions of chromenes **1a–c** with phenyliodonium ylide **2a**




| Entry | Chromene | $R^1$ | $R^2$ | Product[a] | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | **1a** | H | H | **3a** | 67 |
| 2 | **1b** | OMe | H | **3b** | 88 |
| 3 | **1c** | H | OMe | **3c** | 79 |

[a] Reaction conditions: 2*H*-chromene **1** (1 equiv), ylide **2a** (4.5 equiv), $Rh_2(esp)_2$ (0.3 mol %).
[b] Isolated yields.

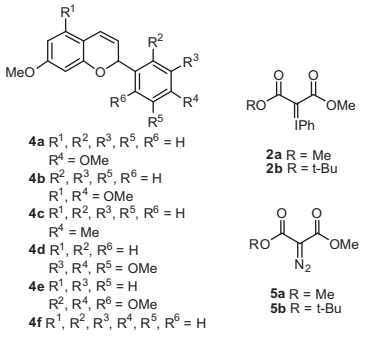


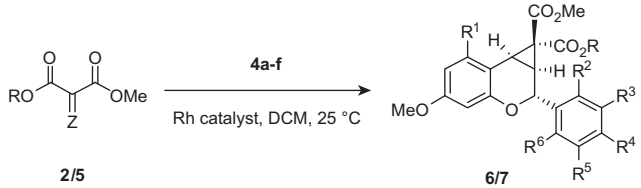

**Figure 1.** Reactants used for the study.

lower yields.[13] Charette has recently reported an improved method for preparing and isolating iodonium ylides of dialkyl malonates.[11] Using $Rh_2(esp)_2$ as catalyst, impressive yields of cyclopropanations of a variety of alkene donors were reported.[11] Applying these conditions to 2*H*-chromenes **1a–c**, we observed good yields of cyclopropane diester products with reagent **2a** (Table 1). Moreover, reactions were complete after 2 h, compared to 12–16 h typically required when diazo compounds were used.[8] This suggested to us that these reagents might be a viable alternative to α-diazo esters for cyclopropanating the more sterically hindered 2-aryl-substituted chromenes.

To test this, compounds **4a–f** (Fig. 1) were prepared using the method of Nagata and co-workers.[14] While the lability of 2-aryl-2*H*-chromenes has been well documented,[15] most of the chromenes we prepared were found to be moderately stable when stored under inert atmosphere at low temperature. Those that were prone to decomposition, such as **4d** and **4e**, were used immediately following their synthesis. In addition to ylide **2a**, reagents **2b**, **5a**, and **5b**, were also prepared according to published procedures from dimethyl- and *tert*-butyl methyl malonates.[11,16] To the best of our knowledge, compound **2b** had not been previously reported. Because the iodonium ylides had a very short shelf-life, even when stored at −10 °C under inert atmosphere, they were used immediately to avoid decomposition.

Studying cyclopropanations of styrene, Charette and co-workers reported superior yields of products using phenyliodonium ylides of malonate esters compared with their diazo counterparts.[11] However, we noticed that only $Rh(OAc)_4$ was used as the catalyst with the diazo reagents. We therefore decided to first study the reactions of derivative **4a** with *tert*-butyl methyl α-diazomalonate **5b** in the presence of different rhodium catalysts to optimize the formation of derivative **6a** (Table 2). As expected,

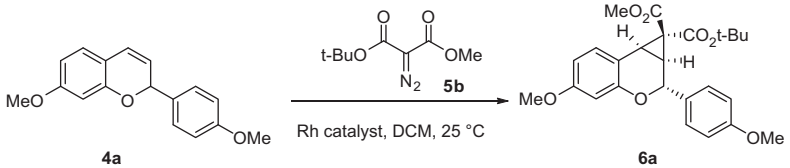
**Table 3**
Reactions of chromenes **4a–f** with reagents **2** and **5**




| Entry | Chromene | Reagent | R | Z | Catalyst | Product[a] | Yield[b] (%) |
|---|---|---|---|---|---|---|---|
| 1 | **4b** | **5b** | *t*-Bu | $N_2$ | $Rh_2$(S-TBSP)$_4$ | **6b** | 68 (84)[c] |
| 2 | **4c** | **5b** | *t*-Bu | $N_2$ | $Rh_2$(S-TBSP)$_4$ | **6c** | 65 |
| 3 | **4f** | **5b** | *t*-Bu | $N_2$ | $Rh_2$(S-TBSP)$_4$ | **6f** | 47 |
| 4 | **4a** | **5a** | Me | $N_2$ | $Rh_2$(S-TBSP)$_4$ | **7a** | 50 |
| 5 | **4b** | **5a** | Me | $N_2$ | $Rh_2$(S-TBSP)$_4$ | **7b** | 78 |
| 6 | **4c** | **5a** | Me | $N_2$ | $Rh_2$(S-TBSP)$_4$ | **7c** | 61 |
| 7 | **4d** | **5b** | *t*-Bu | $N_2$ | $Rh_2$(S-TBSP)$_4$ | None | — |
| 8 | **4e** | **5b** | *t*-Bu | $N_2$ | $Rh_2$(S-TBSP)$_4$ | None | — |
| 9 | **4c** | **2a** | Me | IPh | $Rh_2(esp)_2$ | **7c** | 84 |
| 10 | **4a** | **2a** | Me | IPh | $Rh_2(esp)_2$ | **7a** | 95 |
| 11 | **4d** | **2a** | Me | IPh | $Rh_2(esp)_2$ | **7d** | 49 |
| 12 | **4e** | **2a** | Me | IPh | $Rh_2(esp)_2$ | **7e** | 52 |
| 13 | **4a** | **2b** | *t*-Bu | IPh | $Rh_2(esp)_2$ | None | — |
| 14 | **4b** | **2b** | *t*-Bu | IPh | $Rh_2(esp)_2$ | None | — |
| 15 | **4c** | **2b** | *t*-Bu | IPh | $Rh_2(esp)_2$ | None | — |

[a] Diastereomeric purity established by $^1$H NMR.
[b] Isolated yields.
[c] Yield based on recovered chromene.

**Table 2**
Formation of cyclopropane diester **6a** from chromene **4a** using different rhodium catalysts




| Entry | Catalyst | Yield of **6a**[a] (%) |
|---|---|---|
| 1 | $Rh_2(OAc)_4$ | 13 |
| 2 | $Rh_2(CF_3CF_2CF_2CO_2)_4$ | 27 |
| 3 | $Rh_2$(S-PTAD)$_4$ | 15 |
| 4 | $Rh_2(esp)_2$ | No Rxn |
| 5 | $Rh_2$(S-TBSP)$_4$ | 67[b] |

[a] Isolated yields.
[b] Reaction conditions: 2*H*-chromene **4a** (1 equiv), diazoester **5b** (3 equiv), Rh catalyst (1 mol %), 12–16 h.

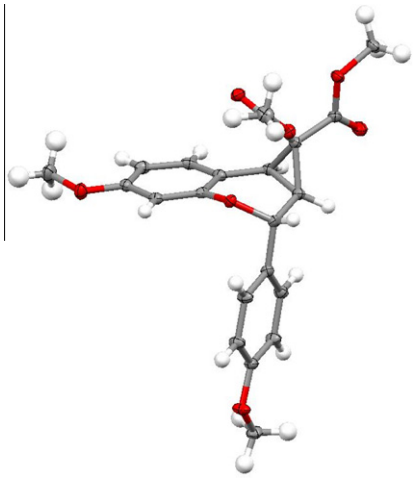
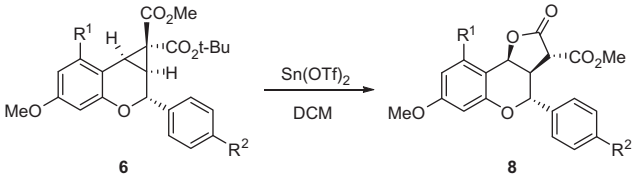


**Figure 2.** The X-ray crystal structure of **7a**.

**Table 4**
$Sn(OTf)_2$ initiated rearrangement of cyclopropane diesters **6** to γ-lactones **8**




6 8

| Entry | Cyclopropane | $R^1$ | $R^2$ | Product | Yield (%) |
|---|---|---|---|---|---|
| 1 | **6a** | H | OMe | **8a** | 75 |
| 2 | **6b** | OMe | OMe | **8b** | 53 |
| 3 | **6c** | H | Me | **8c** | 66 |
| 4 | **6f** | H | H | **8f** | 74 |

$Rh_2(OAc)_4$ gave disappointing results, as did three other catalysts (entries 1–4). However, $Rh_2$(S-TBSP)$_4$ gave a satisfactory yield of the desired product (entry 5). In addition to the 1,1-cyclopropane diester product **6a**, formation of the carbene dimer was an unavoidable by-product which fortunately could be separated by column chromatography. In order to achieve complete cyclopropanation of **4a**, 3 equiv of **5b** were required.

These conditions were found to be general for most reactions studied (Table 3, entries 1–6). The exceptions were compounds **4d** and **4e** which failed to react with diazo derivative **5b** (entries 7 and 8). As noted earlier, these trimethoxyaryl-substituted chromenes were found to be highly susceptible to decomposition and were used immediately. However, we suspected that their lack of reactivity might have been due to their higher rate of decomposition relative to cyclopropane formation which required 12–16 h to complete. The chromenes **4d** and **4e** were equally unreactive to reagent **5a**, suggesting the reaction duration was a factor in these reactions. Indeed, the faster reacting iodonium ylide **2a** gave cyclopropane products with both **4d** and **4e**, albeit in moderate yield (Table 3, entries 11 and 12). In these cases, we surmise that reactions were able to progress significantly before substantial decomposition of the chromene occurred. Moreover, reactions with ylide **2a** in general gave higher yields of cyclopropane products than their diazo counterparts (Table 2, entries 9 and 10). To our surprise, however, no reaction was observed when reagent **2b** was used, in which one of the ester groups was *tert*-butyl (Table 3, entries 13–15). This was somewhat disappointing, in light of the fact that the iodonium ylide of di*tert*-butyl malonate has been shown to add to styrene.[11]

In every case, the 1,1-cyclopropane diester formed as a single diastereomer, and not surprisingly the X-ray crystal structure of **7a** showed that cyclopropanation occurred anti to the C2-aryl substituent (Fig. 2). As an added note, because $Rh_2$(S-TBSP)$_4$ is chiral, we checked for enantiomeric enrichment in the products formed in the presence of this catalyst. However, we found no evidence of kinetic resolution in these reactions.

As expected, cyclopropanes substituted with a *tert*-butyl ester group rearranged to γ-lactone on treatment with $Sn(OTf)_2$ (Table 4). In comparison, the corresponding 1,1-dimethyl ester derivatives gave multiple products on treatment with a variety of Lewis acids ($TiCl_4$, $BF_3$, $Sc(OTf)_3$, $Sn(OTf)_2$). We are currently investigating the use of these lactones in the synthesis of biflavonoid natural products.

In conclusion, iodonium ylides and α-diazo derivatives of dialkyl malonates serve complimentary roles in the formation of 1,1-cyclopropane esters from 2-aryl-2*H*-chromenes. Diazo compounds are the preferred reagents for forming tetrahydro-2*H*-furochromenones, because of the need for a *tert*-butyl ester group to facilitate the rearrangement step. However, the choice of catalyst is critical. In contrast, superior yields of *gem*-dimethyl esters are obtained using the iodonium ylide **2a** (see Table 3). These donor–acceptor cyclopropanes should lend themselves to a multitude of transformations, hopefully yielding a variety of novel aryl-substituted chroman structures.[17]

## Acknowledgements

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## Supplementary data

The crystallographic data was deposited with the Cambridge Crystallographic Data Centre (deposition number CCDC 876447) and can be obtained free of charge from www.ccdc.cam.ac.uk.

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.061.

## References and notes

1. (a) Gupta, A.; Mandal, S. K.; Leblanc, V.; Descoteaux, C.; Asselin, E.; Berube, G. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3982–3987; (b) Constantinou, A. I.; Husband, A. *Anticancer Res.* **2002**, *22*, 2581–2585; (c) LaLonde, R. T.; Ramdayal, F.; Sarko, A.; Yanai, K.; Zhang, M. *J. Med. Chem.* **2003**, *46*, 1180–1190.
2. Gafner, S.; Bergeron, C.; Villinski, J. R.; Godejohann, M.; Kessler, P.; Cardellina, J. H.; Ferreira, D.; Feghali, K.; Grenier, D. *J. Nat. Prod.* **2011**, *74*, 2514–2519.
3. Sawadjoon, S.; Kittakoop, P.; Kirtikara, K.; Vichai, V.; Tanticharoen, M.; Thebtaranonth, Y. *J. Org. Chem.* **2002**, *67*, 5470–5475.
4. (a) Luan, Yi.; Sun, H.; Schaus, S. E. *Org. Lett.* **2011**, *13*, 6480–6483; (b) Devakaram, R.; Black, D. StC.; Andrews, K. T.; Fisher, G. M.; Davis, R. A.; Kumar, N. *Bioorg. Med. Chem.* **2011**, *19*, 5199–5206.
5. Deng, J.-Z.; Starck, S. R.; Li, S.; Hecht, S. M. *J. Nat. Prod.* **2005**, *68*, 1625–1628.
6. For recent activity in this area, see Ref.[4] and Korotaev, V. Yu.; Sosnovskikh, V. Ya.; Barabanov, M. A.; Yasnova, E. S.; Ezhikova, M. A.; Kodess, M. I.; Slepukhin, P. A. *Tetrahedron* **2010**, *66*, 1404–1409.
7. For an enantioselective route to 2-aryl-2*H*-chromenes, see: Moquist, P. N.; Kodama, T.; Schaus, S. E. *Angew. Chem., Int. Ed* **2010**, *49*, 7096–7100.
8. Stokes, S.; Spears, B.; Laseter, C.; Barker, B.; Mead, K. T. *Tetrahedron Lett.* **2010**, *51*, 4003–4006.
9. For examples, see: (a) Fristad, W. E.; Peterson, J. R.; Ernst, A. B. *J. Org. Chem.* **1985**, *50*, 3143–3148; (b) del Rosario-Chow, M.; Ungwitayatorn, J.; Currie, B. L. *Tetrahedron Lett.* **1991**, *32*, 1011–1014; (c) D'Annibale, A.; Trogolo, C. *Tetrahedron Lett.* **1994**, *35*, 2083–2086; (d) Allegretti, M.; D'Annibale, A.; Trogolo, C. *Tetrahedron* **1993**, *49*, 10705–10714.
10. For related reaction sequences, see: (a) Kim, C.; Brady, T.; Kim, S. H.; Theodorakis, E. A. *Synth. Commun.* **2004**, *34*, 1951–1965; (b) Davies, H. M. L.; Hu, B. *J. Org. Chem.* **1992**, *57*, 4309–4312.

11. Goudreau, S. R.; Marcoux, D.; Charette, A. B. *J. Org. Chem.* **2009**, *74*, 470–473.
12. Batsila, C.; Kostakis, G.; Hadjiarapoglou, L. P. *Tetrahedron Lett.* **2002**, *43*, 5997–6000.
13. (a) Moreau, B.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 18014–18015; (b) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2313–2316; (c) Müller, P.; Ghanem, A. *Org. Lett.* **2004**, *6*, 4347–4350; (d) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2003**, *5*, 2327–2329.
14. Ashihara, Y.; Nagata, Y.; Kurosawa, K. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3298–3301.
15. (a) Vaiana, N.; Rizzi, L.; Pezzano, M. G.; Restelli, R.; Rota, F.; Stefanini, S.; Vicentini, S.; Romeo, S. *Lett. Org. Chem.* **2007**, *4*, 288–291; (b) Nay, B.; Peyrat, J.-F.; Vercauteren, J. *Eur. J. Org. Chem.* **1999**, 2231–2234; (c) Tückmantel, W.; Kozikowski, A. P., ; Romanczyk, L. J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 12073–12081.
16. Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. *Synth. Commun.* **1987**, *17*, 1709–1716.
17. For recent examples of donor-acceptor cyclopropanes in synthesis, see: (a) Gharpure, S. J.; Vijayasree, U.; Reddy, S. R. B. *Org. Biomol. Chem.* **2012**, *10*, 1735–1738; (b) Sathishkannan, G.; Srinivasan, K. *Org. Lett.* **2011**, *13*, 6002–6005; (c) Parsons, A. T.; Smith, A. G.; Neel, A. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2010**, *132*, 9688–9692; (d) Moustafa, M. M. A. R.; Stevens, A. C.; Machin, B. P.; Pagenkopf, B. L. *Org. Lett.* **2010**, *12*, 4736–4738.