Lewis acid-catalyzed diastereoselective hydroarylation of benzylidene malonic esters

Shaofeng Duan, **Ranjan Jana**, and **Jon A. Tunge**[*]
Department of Chemistry, 1251 Wescoe Hall Drive, 2010 Malott Hall, The University of Kansas, Lawrence, Kansas 66045-7582 and the KU Chemical Methodologies and Library Development Center of Excellence.

Abstract
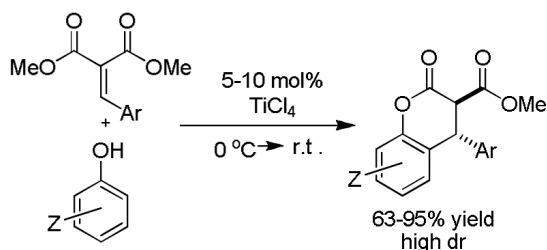
Herein we report that simple Lewis acids catalyze the hydroarylation of benzylidene malonates with phenols. Ultimately, 3,4-disubstituted dihydrocoumarins are obtained via a hydroarylation-lactonization sequence. Moreover, the dihydrocoumarins are formed with a high degree of diastereoselectivity favoring the *trans* stereoisomer.

Hydroarylation of cinnamic acid derivatives is a powerful method for the formation of synthetically versatile dihydrocoumarin derivatives.[1,2,3] However, such hydroarylations are commonly carried out in highly acidic media and the substrate scope can be limited.[2] For example, the CF_3CO_2H-catalyzed hydroarylation of cinnamic acids is limited to electron-rich cinnamic acids.[2b] Thus, we are interested in developing methods for the hydroarylation of electron deficient cinnamic acid derivatives. First, it was necessary to explain why electron-deficient cinnamates, which are inherently more electrophilic than electron rich cinnamates, are much less reactive toward acid-catalyzed arylation with phenols. We reasoned that while electron-deficient cinnamates are inherently more reactive toward nucleophilic attack by phenols, they are poorly activated by acid catalysts due to their low basicity (Scheme 1). In other words, the slow rates of hydroarylation of electron-deficient cinnamates are likely attributed to the inability to activate the cinnamic acid/ester via protonation.

With this in mind, we reasoned that the degree of protonation could be increased by appending another donor group that would stabilize the protonated intermediate via intramolecular hydrogen bonding (Scheme 2). A pendant carboxyl group was seen as ideal since it can activate the substrate toward catalytic hydroarylation, yet can be easily removed by decarboxylation.[4] Thus, we began by examining the hydroarylation of an electron-deficient benzylidene malonates under our previously reported conditions for hydroarylation.[2b] Related catalytic

---

[*]tunge@ku.edu .

hydroarylation of benzylidene malonates with good nucleophiles like indole are known,[5] however, that chemistry has not been extended to the use of phenols, which are significantly less nucleophilic than indoles.

Initially, dimethyl (*p*-nitrobenzylidene)malonate was chosen as a model electron-deficient olefin for hydroarylation (Scheme 3). Allowing the olefin **1a** to react with 3,5-dimethoxyphenol in CH_2Cl_2 in the absence of catalyst produced no product after 7 days at room temperature. When a catalytic amount of trifluoroacetic acid (TFA) was added, then 29% conversion to dihydrocoumarin **2a** was realized after 30 hours. Increasing the amount of "catalyst" so that the reaction was run in neat TFA did allow for 90% conversion of the starting material, however these conditions produced a 2.4:1 ratio of cyclic (**2a**) and acyclic (**3a**) hydroarylation products. While TFA proved to be relatively in effective as a hydroarylation catalyst, the observation of any hydroarylation products indicates that the use of benzylidene malonic esters does indeed facilitate the acid-catalyzed hydroarylation of electron-deficient olefins.

Next, we turned our attention to the use of Lewis acid catalysts for hydroarylation of benzylidene malonates (Table 1). While $MgBr_2$ and $ZnCl_2$ were effective catalysts for the reaction, stronger Lewis acids did indeed effect complete conversion to the product dihydrocoumarin in a reasonable amount of time. Ultimately, $TiCl_4$, $Cu(OTf)_2$, and Sc $(OTf)_3$ were identified as potentially practical catalysts. Each of these catalysts provided the desired product in high yield as well as high diastereoselectivity. That said, transesterification to the dihydrocoumarins was not as effective with $Cu(OTf)_2$. Thus, while hydroarylation products of **1a** with 3,5-dimethoxyphenol were formed in 98% combined yield, 39% of that mixture was the uncyclized dimethylmalonate derivative **3a**; this uncyclized product was not observed when other Lewis acid catalysts were employed. Further comparison of the catalysts with a less electron-rich phenol (benzo[1,3]dioxol-5-ol) provided product **2b**, however these studies revealed that $TiCl_4$ is a more active catalyst than either $Cu(OTf)_2$ or $Sc(OTf)_3$. Once again, the reactions are highly diastereoselective. Moreover, the phenol reacts regioselectively at the least hindered *ortho*-position (i.e. the 6-position) of the phenol.[6] Several other phenols were briefly investigated and, in each case, $TiCl_4$ was the most active catalyst and hydroarylation always proceeded at the least hindered *ortho*-position of the phenol.[7] One limitation is the requirement that the phenol is electron rich; no reaction is observed between the electron deficient olefin **1a** and phenol.

Having demonstrated that $TiCl_4$ is the most active catalyst for hydroarylation of benzylidene malonates with phenols, we turned our attention to investigating the scope of benzylidene malonates that will undergo hydroarylation (Table 2). Importantly, both electron donating and electron withdrawing functional groups are tolerated on the benzylidene malonate. Moreover, even highly electron-deficient benzylidene malonates (**2q, 2r**) are excellent substrates for the catalytic hydroarylation. There is also a fair degree of functional group tolerance, with nitro groups, ethers, esters, and halogens all proving to be compatible with the reaction conditions. Furthermore, the functional groups can be incorporated in any of the *o-, m-,* or *p*-positions of the benzylidene malonate. Taken together these data show that the hydroarylation of benzylidene malonates is not very sensitive to the sterics or electronics of the arene rings of the benzylidene malonates.

At this point it was still unclear whether the major diastereomer was the *cis* or the *trans* isomer. The vicinal coupling constants for products (J_{HH}) are small (ca. 1-2 Hz), but this coupling constant is ambiguous given the fact that these products do not rigorously adopt chair conformations. In fact, simple molecular modeling using the MM2 force field suggests that the H-C-C-H dihedral angle for the *trans* diastereomer is 73°, while that in the *cis* isomer is 52°.[8] Using simple Karplus analysis suggests that the *trans* diastereomer should have a coupling constant of 0.8 Hz, while the *cis* isomer should have a coupling constant of 2.3 Hz.

[9] The observed coupling constant for **2a** (J_{2a} = 1.5 Hz) does not clearly distinguish between these two possibilities.. A further result of the molecular mechanics simulations is that the *trans* diastereomer is favored by ca. 10 kcal/mol and is expected to adopt a half-chair structure where the arene and the ester groups occupy pseudo-axial sites. To test these predictions, and provide unambiguous evidence for the stereochemistry of the diastereomer that is formed, X-ray quality crystals of **2a** were grown and analyzed. The crystal structure confirms that the *trans*-diastereomer is the major product and also confirms the *trans*-pseudo diaxial structure predicted by the MM2 simulations (Fig. 1).[10]

The overall process for formation of dihydrocoumarins from phenols and the benzylidene malonates involves two general transformations: hydroarylation and transesterification. Thus, the reaction could proceed by transesterification followed by intramolecular hydroarylation (path A, Scheme 4) or by intermolecular hydroarylation followed by intramolecular transesterification (path B, Scheme 4). To gain a better mechanistic understanding, ester **1f** (intermediate A in Scheme 4) was prepared. Subjecting ester **1f** to 10 mol% TiCl$_4$ for 48 h, produced no dihydrocoumarin product; only E/Z isomerization of the ester to a 1:1 *E:Z* mixture was observed (Scheme 5). Since ester **1f** is not a kinetically competent catalytic intermediate, path A can be ruled out. Thus, hydroarylation/transesterification (path B) is the most likely mechanism for the formation of dihydrocoumarins. That path B is favored over path A make sense since phenols are much more nucleophilic than benzoate derivatives like that present in **1f**.

Next it was reasoned that, if C-C bond formation occurs before formation of the lactone, it should be possible to observe the acyclic "intermediate B" if one constrains the intermediate so it cannot undergo the cyclization reaction. With this in mind, a constrained coumarin electrophile (**1s**) was subjected to our conditions for titanium-catalyzed hydroarylation (Scheme 6). Indeed, the relative rigidity of the coumarin ring does not allow the substituents to cyclize, and the acyclic phenol is formed exclusively. More specifically, cyclization cannot take place because the *trans*-pseudo-diaxial ester and phenol are not able to achieve a conformation that would allow cyclization. Ultimately, the observation of **2s** supports the hypothesis that the formation of **2a-r** takes place via intermolecular hydroarylation followed by intramolecular transesterification (path B, Scheme 4).

In conclusion, the use of benzylidene malonates facilitates the Brønsted- and Lewis-acid catalyzed arylation by phenols. Titanium tetrachloride was identified as the most practical catalyst for the diastereoselective hydroarylation of benzylidene malonates to produce *trans*-substituted dihydrocoumarins. Finally, mechanistic studies suggest that the reaction proceeds via hydroarylation followed by transesterification. Uses of these intermediates in the synthesis of chemical libraries are being explored.

Experimental Section

General procedure for the TiCl$_4$-catalyzed hydroarylation of benzylidene malonates with phenols

Phenol (0.25 mmol) and benzylidene malonate (0.25 mmol) were dissolved completely in dry dichloromethane (2 mL) to form a clear solution which was then cooled to 0 °C. To the solution was added TiCl$_4$ via a syringe. After reaction completion was indicated by TLC, 1N HCl (10 mL) was added and the mixture was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were washed with water (5 mL), saturated sodium bicarbonate (5 mL) and brine (5 mL), and then dried over magnesium sulfate. Concentration under reduced pressure gave a crude product which was purified via flash chromatography.

Methyl 5,7-dimethoxy-4-4-nitrophenyl)-2-oxochroman-3-carboxylate (2a)

Compound **2a** was isolated as a white solid. IR v_{max} (neat) / cm^{-1}: 1776, 1744, 1626, 1595, 1522, 1350; ^{1}H NMR (400MHz, CDCl$_3$): δ 3.72 (3H, s), 3.75 (3H, s), 3.83(3H, s), 3.96 (1H, d, *J* = 1.6), 5.08 (1H, s), 6.30 (1H, d, *J* = 2.0), 6.37 (1H, d, *J* = 2.4), 7.31 (2H, d, *J* = 8.8), 8.14 (2H, d, *J* = 8.8); ^{13}C NMR (100MHz, CDCl$_3$): δ 38.6, 53.6, 53.6, 55.6, 55.9, 94.0, 95.6, 102.1, 124.3, 128.1, 147.1, 147.3, 152.5, 157.7, 161.6, 163.0, 166.7; HRMS (ESI): Calcd. for C$_{19}$H$_{17}$NO$_8$Na (M + Na$^+$): 410.0852. Found: 410.0857.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1(a). Neugebauer RC, Uchiechowska U, Meier R, Hruby H, Valkov V, Verdin E, Sippl W, Jung M. J. Med. Chem 2008;51:1203–1213. [PubMed: 18269226] (b) Li K, Tunge JA. J. Comb. Chem 2008;10:170–174. [PubMed: 18237144] (c) Srinivas K, Srinivasan N, Reddy KS, Ramakrishna M, Reddy CR, Arunagiri M, Kumari RL, Venkataraman S, Mathad VT. Org. Proc. Res. Dev 2005;9:314–318. (d) Awale S, Tezuka Y, Wang S, Kadota S. Org. Lett 2002;4:1707–1709. [PubMed: 12000279]

2(a). Rodrigues-Santos CE, Echevarria A. Tetrahedron Lett 2007;48:4505–4508. (b) Li, Kelin; Foresee, LN.; Tunge, JA. J. Org. Chem 2005;70:2881–2883. [PubMed: 15787594] (c) Majumder PL, Chatterjee S, Mukhoti NJ. Ind. Chem. Soc 2001;78:743–755. (d) Dupin J-FE, Chenault J. Heterocycles 1983;20:2401–2404. (e) Camps F, Coll J, Colomina O, Messeguer A. J. Heterocyclic Chem 1985;22:363–368.

3(a). Shaabani A, Soleimani E, Rezayan AH, Sarvary A, Khavasi HR. Org. Lett 2008;10:2581–2584. [PubMed: 18503292] (b) Richardson TI, Dodge JA, Durst GL, Pfeifer LA, Shah J, Wang Y, Durbin JD, Krishnan V, Norman BH. Biorg. Med. Chem. Lett 2007;17:4824–4828. (c) Piao C-R, Zhao Y-L, Han X-D, Liu Q. J. Org. Chem 2008;73:2264–2269. [PubMed: 18290661]

4. Patra A, Misra SK. Indian J. Chem., Sect. B 1988;27B:272–273.

5(a). Zhuang W, Hansen T, Jorgensen KA. Chem. Commun 2001:347–348. (b) Zhou J, Tang Y. Chem. Commun 2004:432–433.

6. Ziegler T, Moehler H, Effenberger F. Chem. Ber 1987;120:373–378.

7(a). Labaudiniere L, Burgada R. Tetrahedron 1986;42:3521–3536. (b) Bharate SB, Khan SI, Yunus NAM, Chauthe SK, Jacob MR, Tekwani BL, Khan IA, Singh IP. Bioorg. Med. Chem 2007;15:87–96. [PubMed: 17070063]

8. Using CambridgeSoft ChemBio3D.

9. Karplus, Martin. J. Am. Chm. Soc 1963;85:2870–2871.

10. The aliphatic H-C-C-H dihedral angle is 81° in the crystal compared to 72° that was predicted based on MM2 calculations.
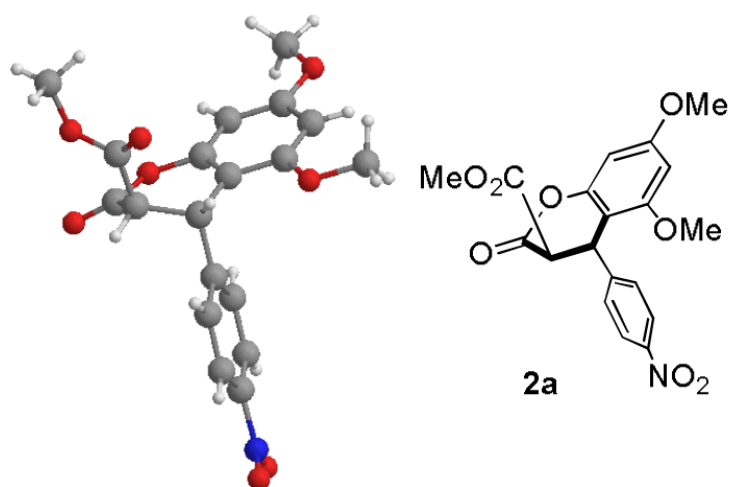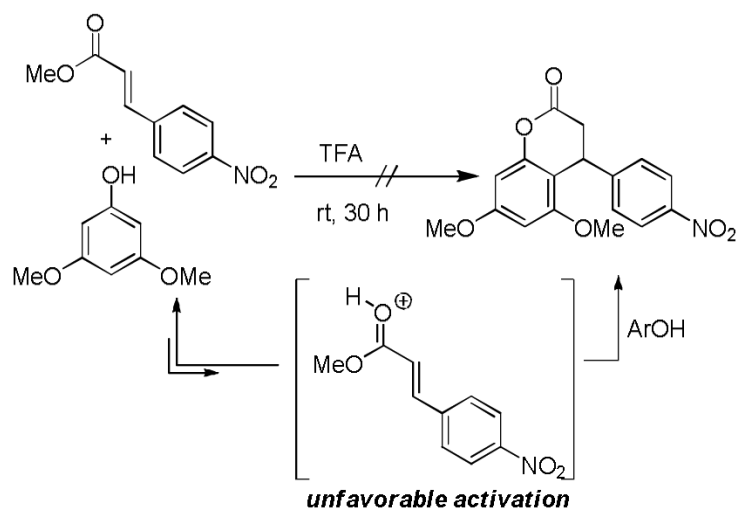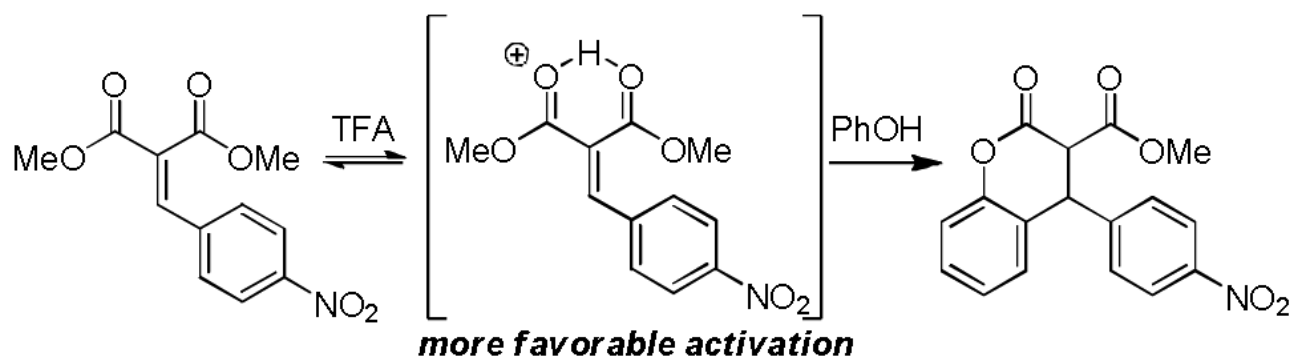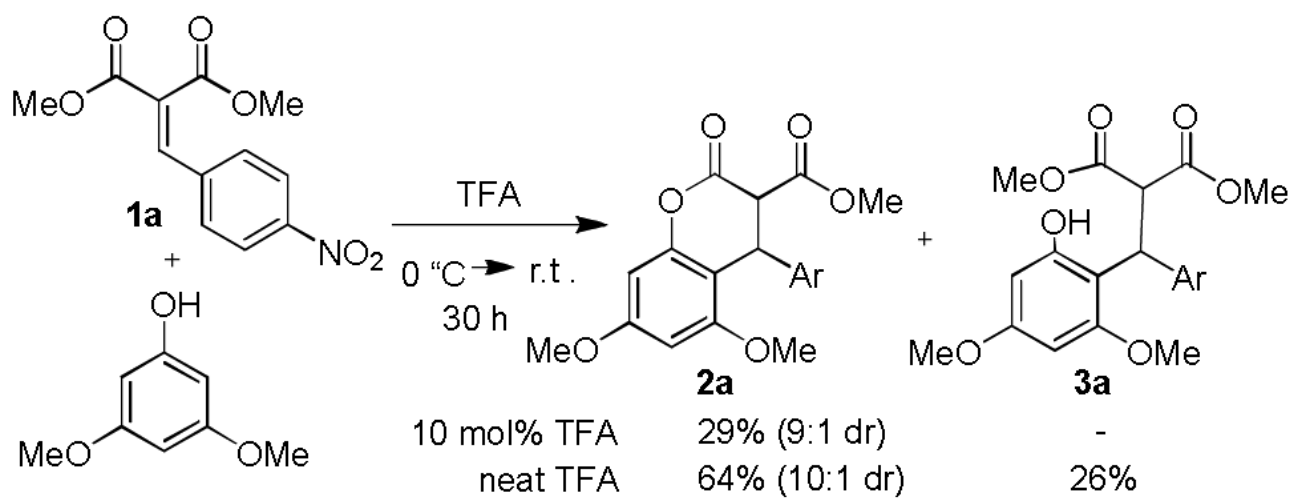
Figure 1.
Crystal structure of 2a

Scheme 1.
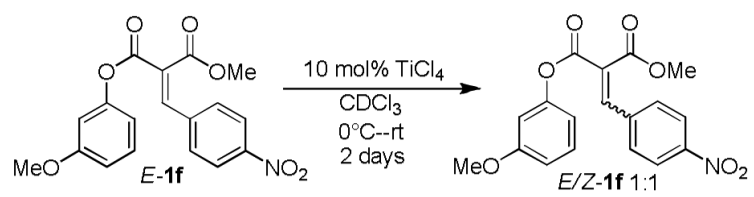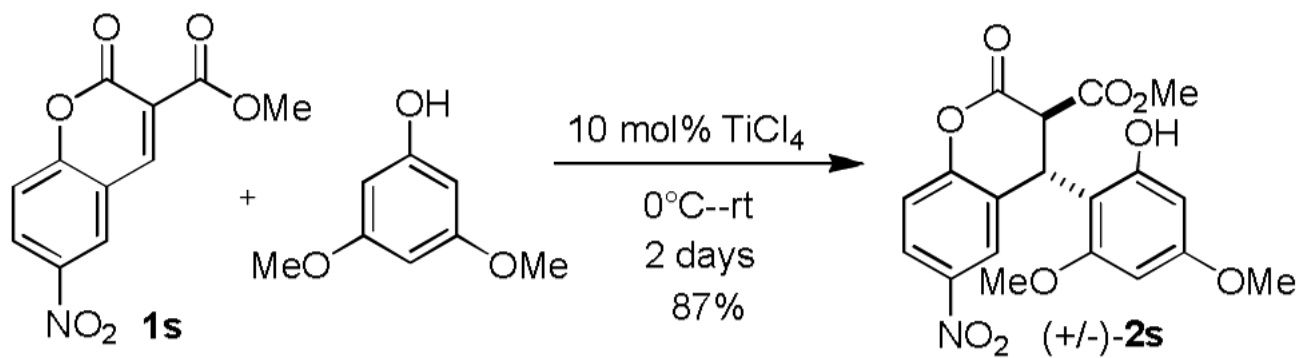
Scheme 2.

Scheme 3.
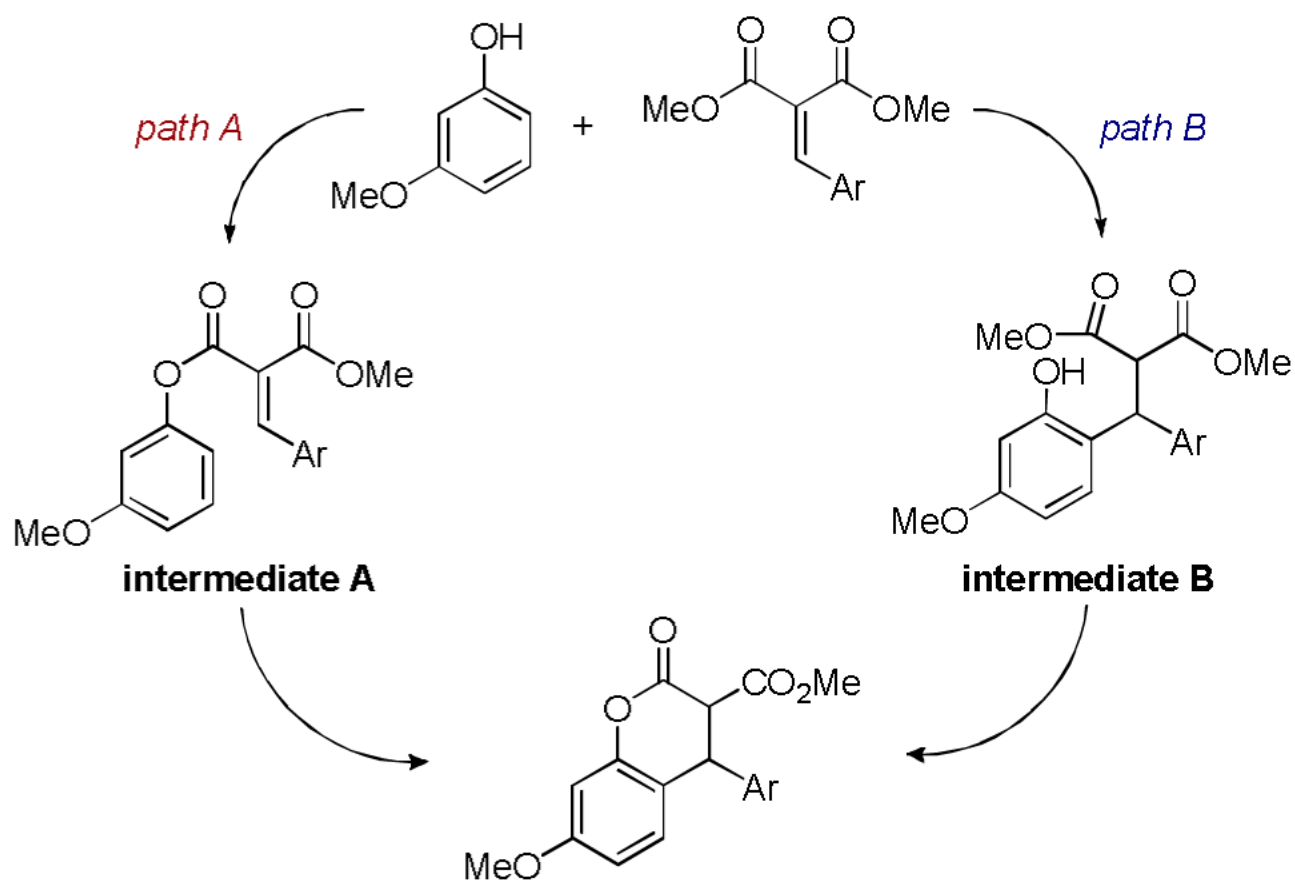
Scheme 4.

Scheme 5.

Scheme 6.

Table 1

Catalysts for hydroarylation

product	catalyst	loading	time	dr	yield[a]
	none	-	7d	-	NR
	TFA	10 mol%	30h	9:1	29%
	TiCl$_4$	5 mol%	30h	20:1	86%
	Cu(OTf)$_2$	5 mol%	30h	17:1	98%[b]
	Sc(OTf)$_3$	5 mol%	30h	>20:1	85%
	Bi(OTf)$_3$	10 mol%	14d	>20:1	90%
	TiCl$_4$	5 mol%	36h	15:1	85%
	Cu(OTf)$_2$	5 mol%	36h	>20:1	71%
	Sc(OTf)$_3$	5 mol%	36h	>20:1	65%
	Bi(OTf)$_3$	10 mol%	14d	20:1	90%
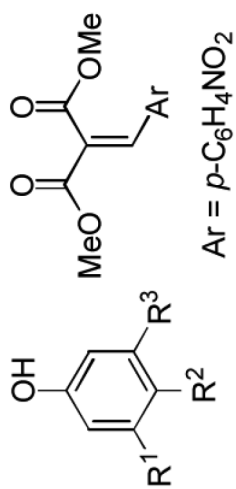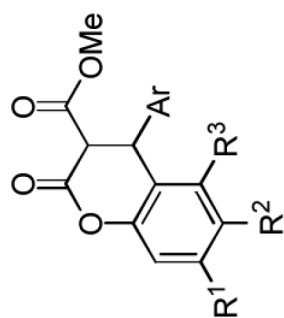
product	catalyst	loading	time	dr	yield[a]
	TiCl$_4$	10 mol%	72h	13:1	87%
	Cu(OTf)$_2$	10 mol%	72h	18:1	79%
	Sc(OTf)$_3$	10 mol%	72h	7:1	86%
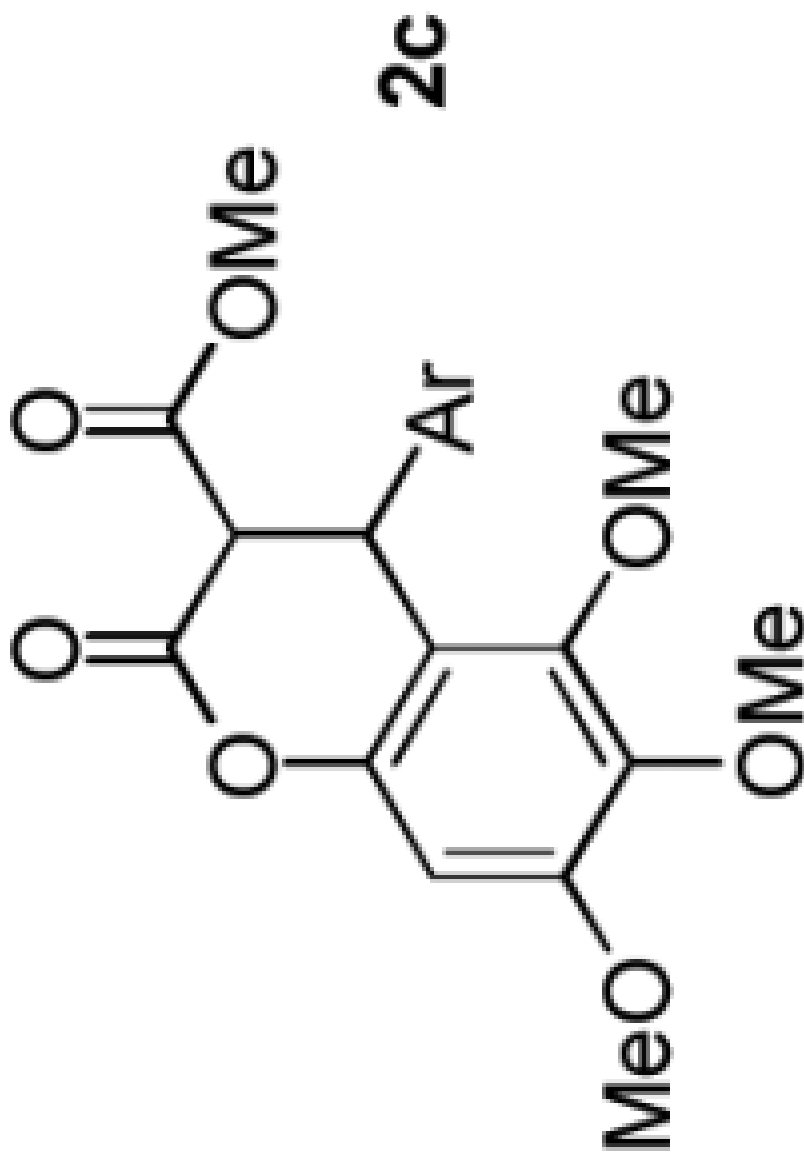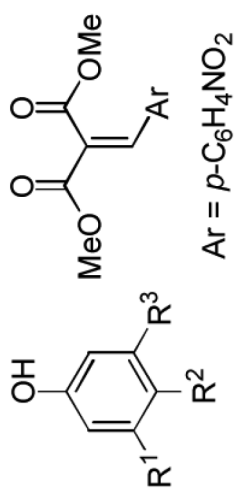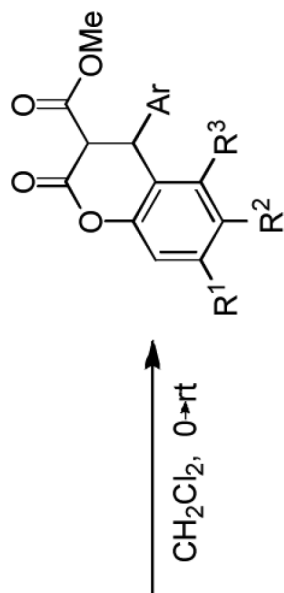
product	catalyst	loading	time	dr	yield[a]
	TiCl$_4$	10 mol%	72h	7:1	81%
	Cu(OTf)$_2$	10 mol%	72h	7:1	86%
	Sc(OTf)$_3$	30 mol%	72h	13:1	80%
	TiCl$_4$	10 mol%	72h	11:1	72%
	TiCl$_4$	5 mol%	30h	>20:1	80%

[a] isolated yields

[b] isolated as a 1.5:1 mixture of **2a:3a**.

Table 2

Scope of benzylidene malonates

product	R_1	R_2	R_3	dr	yield (%)[a]
2g	H	H	Br	22:1	78
2h	CF₃	H	H	>20:1	72 (87)[b]
2i	H	H	CO₂Me	>20:1	74
2j	H	H	H	17:1	85
2k	OMe	H	H	>20:1	90
2l	Br	H	H	>20:1	67
2m	H	OMe	H	>20:1	95
2n	H	H	OMe	17:1	63
2o	OMe	H	OMe	>20:1	78
2p	H	H	Me	>20:1	74 (85)[b]
2q	H	F	F	20:1	95[c]
2r	NO₂	H	NO₂	10:1	77[c]

[a] isolated yields, 0.25 mmol substrate

[b] 10 mol% TiCl4

[c] performed on 3 mmol scale