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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, and the KU Chemical Methodologies and Library Development Center of Excellence, The University of Kansas, Lawrence, Kansas 66045-7582

tunge@ku.edu

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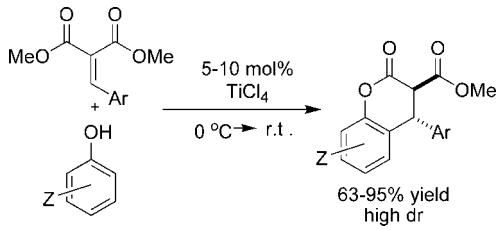
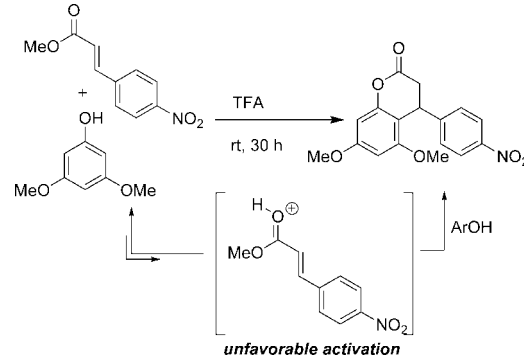


Herein we report that simple Lewis acids catalyze the hydroarylation of benzylidene malonates with phenols. Ultimately, 3,4-disubstituted dihydrocoumarins are obtained via a hydroarylation−lactonization sequence. Moreover, the dihydrocoumarins are formed with a high degree of diastereoselectivity favoring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

Hydroarylation of cinnamic acid derivatives is a powerful method for the formation of synthetically versatile dihydrocoumarin derivatives.[1−3] 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.

SCHEME 1



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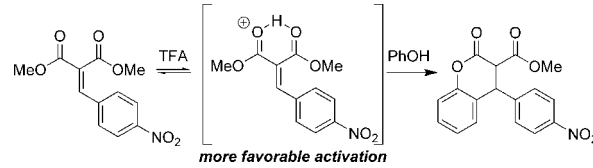

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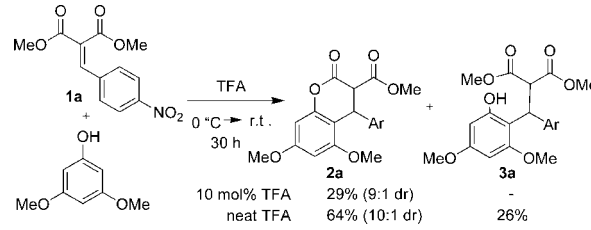

With this in mind, we reasoned that the degree of protonation could be increased by appending another donor group that would stabilize the protonated intermediate via intramolecular hydrogen bonding (Scheme 2). A pendant carboxyl group was seen as ideal since it can activate the substrate toward catalytic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

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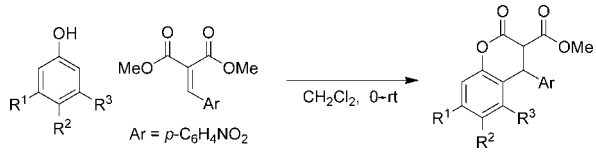
TABLE 1. Catalysts for Hydroarylation



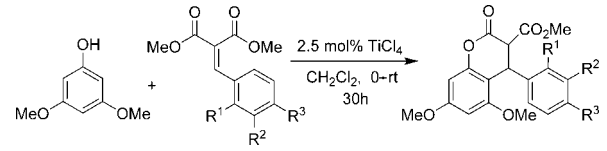
product	catalyst	loading	time	dr	yield[a]
	none	-	7d	-	NR
	TFA	10 mol%	30h	9:1	29%
	$TiCl_4$	5 mol%	30h	20:1	86%
2a	$Cu(OTf)_2$	5 mol%	30h	17:1	98%[b]
	$Sc(OTf)_3$	5 mol%	30h	>20:1	85%
	$Bi(OTf)_3$	10 mol%	14d	>20:1	90%
	$TiCl_4$	5 mol%	36h	15:1	85%
2b	$Cu(OTf)_2$	5 mol%	36h	>20:1	71%
	$Sc(OTf)_3$	5 mol%	36h	>20:1	65%
	$Bi(OTf)_3$	10 mol%	14d	20:1	90%
	$TiCl_4$	10 mol%	72h	13:1	87%
2c	$Cu(OTf)_2$	10 mol%	72h	18:1	79%
	$Sc(OTf)_3$	10 mol%	72h	7:1	86%
	$TiCl_4$	10 mol%	72h	7:1	81%
2d	$Cu(OTf)_2$	10 mol%	72h	7:1	86%
	$Sc(OTf)_3$	30 mol%	72h	13:1	80%
2e R = H	$TiCl_4$	10 mol%	72h	11:1	72%
2f R = Me	$TiCl_4$	5 mol%	30h	>20:1	80%

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

trifluoroacetic acid (TFA) was added, then 29% conversion to dihydrocoumarin **2a** was realized after 30 h. 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 ineffective 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 not 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

TABLE 2. Scope of Benzylidene Malonates



product	R_1	R_2	R_3	dr	yield (%)[a]
2g	H	H	Br	22:1	78
2h	CF_3	H	H	>20:1	72 (87)[b]
2i	H	H	CO_2Me	>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	NO_2	H	NO_2	10:1	77[c]

[a] isolated yields, 0.25 mmol substrate. [b] 10 mol % $TiCl_4$ [c] performed on 3 mmol scale.

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 ortho, meta, or para 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] 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

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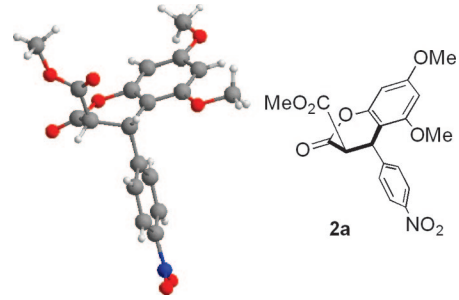
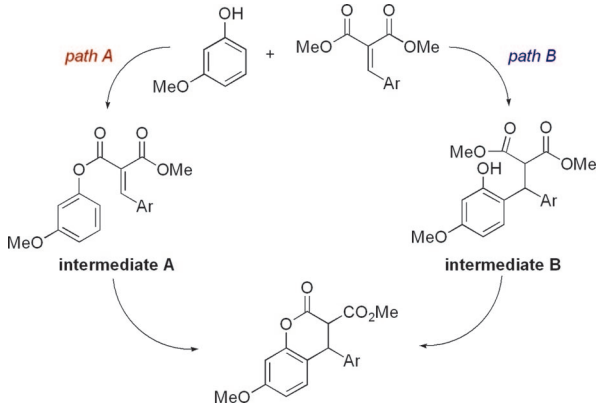
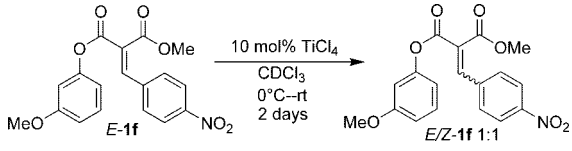


FIGURE 1. Crystal structure of **2a**.

SCHEME 4



SCHEME 5

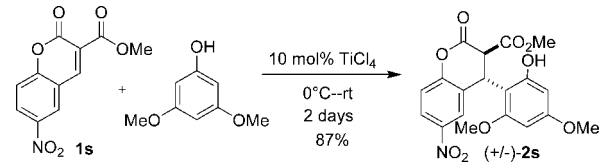


possibilities. A further result of the molecular mechanics simulations is that the trans diastereomer is favored by ca. 10 kcal/mol and is expected to adopt a half-chair structure where the arene and the ester groups occupy pseudoaxial sites. To test these predictions, and provide unambiguous evidence 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 (Figure 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 % of $TiCl_4$ 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 makes

(10) The aliphatic H−C−C−H dihedral angle is 81° in the crystal structure, compared to 72° that was predicted based on MM2 calculations.

SCHEME 6



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 is 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 that was then cooled to 0 °C. To the solution was added $TiCl_4$ via a syringe. After reaction completion was indicated by TLC, 1 N 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 that 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 ν_{max} (neat)/cm^{-1} 1776, 1744, 1626, 1595, 1522, 1350; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (3H, s), 3.75 (3H, s), 3.83 (3H, s), 3.96 (1H, d, J = 1.6 Hz), 5.08 (1H, s), 6.30 (1H, d, J = 2.0 Hz), 6.37 (1H, d, J = 2.4 Hz), 7.31 (2H, d, J = 8.8 Hz), 8.14 (2H, d, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{19}H_{17}NO_8Na$ (M + Na^+) 410.0852, found 410.0857.

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Supporting Information Available: General experimental and complete compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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