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Organocatalytic Diastereo- and Enantioselective Michael Addition Reactions of 5-Aryl-1,3-dioxolan-4-ones

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ABSTRACT



5-Aryl-1,3-dioxolan-4-one heterocycles derived from mandelic acid derivatives and hexafluoroacetone have been identified as new and effective pro-nucleophiles in highly diastereo- and enantioselective Michael addition reactions to nitro olefins catalyzed by bifunctional epi-9-amino-9-deoxy cinchona alkaloid derivatives. Diastereoselectivities up to 98% and enantioselectivities up to 89% for a range of nitro olefins and 5-aryl-1,3-dioxolan-4-ones under mild reaction conditions are reported.

Single enantiomer bifunctional organocatalysts derived from cinchona alkaloids or cyclohexane diamine have emerged as powerful tools for the enantioselective formation of carbon–carbon and carbon–heteroatom bonds.¹ Their ready preparation and ability to impart high enantiocontrol in the addition of carbon- and heteroatom-centered nucleophiles to a variety of electrophiles have all contributed to the pace of the field.^{2,3} While most efforts have concentrated on the development of the range of electrophilic components, less attention has been devoted to expanding the pool of carbon-centered pro-nucleophiles attuned to this type of catalysis.

§ Pfizer Global Research & Development.

(1) For seminal work, see: (a) Hiemstra, H.; Wynberg, H. J. Am. Chem. Soc. **1981**, 103, 417. (b) Okino, T.; Hoashi, Y.; Takemoto, Y. J. Am. Chem. Soc. **2003**, 125, 12672. (c) Li, H.; Wang, Y.; Tang, L.; Deng, L. J. Am. Chem. Soc. **2004**, 126, 9906. For recent examples, see: (d) Inokuma, T.; Hoashi, Y.; Takemoto, Y. J. Am. Chem. Soc. **2006**, 128, 9413. (e) Li, H.; Wang, Y.-Q.; Deng, L. Org. Lett. **2006**, 8, 4063. To address this, we have been searching for *new and synthetically versatile pro-nucleophilic entities* that would partake in highly stereoselective reactions mediated by metalfree bifunctional catalysts that our group, and others, have developed. One family of heterocycles, the 1,3-dioxolan-4ones, was particularly attractive owing to the simplicity of their structure combined with their ready synthesis (Scheme 1). We postulated that the tunability arising from possible structural and electronic variations to the group at the 5-position and the acetal function could provide the necessary acidity/nucleophilicity profile for some derivatives to partake in enantioselective Lewis base/Brønsted acid bifunctional organocatalyst mediated additions to electrophiles

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⁽²⁾ For reviews, see: (a) Dalko, P. I.; Moisan, L. Angew. Chem., Int. Ed. **2001**, 40, 3726. (b) Shreiner, P. R. Chem. Soc. Rev. **2003**, 32, 289. (c) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. Acc. Chem. Res. **2004**, 37, 621. (d) Takemoto, Y. Org. Biomol. Chem. **2005**, 3, 4299. (e) Taylor, M. S.; Jacobsen, E. N. Angew. Chem., Int. Ed. **2006**, 45, 1520. (f) Connon, S. J. Chem. Eur. J. **2006**, 12, 5418.





(X = Y). Additionally, the use of such pro-nucleophiles would provide adducts with an activated ester moiety, which could undergo hydrolysis, aminolysis, and alcoholysis reactions to yield a range of useful chiral building blocks containing up to two adjacent, and possibly fully substituted, stereocenters.⁴

Here, we present our findings on the use of 5-aryl-1,3dioxolan-4-ones as pro-nucleophiles in the enantioselective organocatalytic Michael addition to nitro olefins. The subsequent manipulation of the adducts, exploiting the natural reactivity of the carbonyl group, is also reported.

Proof of reactivity studies were required to assess whether the acidity/nucleophilicity profile of selected 1,3-dioxolan-4-ones was sufficient for the direct organocatalyzed Michael addition to nitro olefins. A preliminary study was partially

(4) For examples of the use of chiral dioxolan-4-ones in stereoselective Michael reactions, see: (a) Blay, G.; Fernández, I.; Monje, B.; Pedro, J. R.; Ruiz, R. *Tetrahedron Lett.* **2002**, *43*, 8463. (b) Blay, G.; Fernández, I.; Monje, B.; Pedro, J. R. *Tetrahedron* **2004**, *60*, 165. (c) Aitken, R. A.; McGill, S. D.; Power, L. A. *ARKIVOC* **2006**, *7*, 292.



Figure 1. DABCO and cinchonine derived organocatalysts.

encouraging; heterocycle **2a**, derived from mandelic acid and acetone,⁵ reacted with *trans-\beta*-nitrostyrene with DABCO (10%) as catalyst in THF at 30 °C but the conversion was <5% after 14 days (Table 1, entry 1). Ascribing this to an

Table 1.	Catalyst	Screen	and	Reaction	Condition
Optimizat	ion ^a				



entry	cat.	R	solvent	temp (°C)	convn (%) ^b	de (%) ^b	ee (%) ^c
1	$\mathbf{1a}^d$	Me	THF	30	$<5^{e}$		
2	$\mathbf{1a}^d$	CF_3	THF	30	>98 ^f	>98	
3	1c	CF_3	DCM	0	>60 ^g	>80	65
4	1c	CF_3	PhMe	0	$> 98^{h}$	>98	76
5	1c	CF_3	TBME	0	$> 98^{g}$	>85	57
6	1b	CF_3	DCM	0	>80g	>98	43
7	1d	CF_3	DCM	0	$> 98^{g}$	>95	70
8	1e	CF_3	DCM	0	$> 40^{g}$	>90	51
9	1f	CF_3	DCM	0	$> 40^{g}$	>90	26
10	1g	CF_3	DCM	0	$> 85^{g}$	>80	56

^{*a*} Reaction was carried out with **2** (1.0 equiv), **3a** (0.5 equiv), and **1b**-**g** (0.05 equiv) in solvent (1.0 M in **3**). ^{*b*} Determined by ¹H NMR. ^{*c*} Determined by HPLC analysis with a chiral column. ^{*d*} 0.1 equiv used. ^{*e*} After 14 days. ^{*f*} After 96 h. ^{*s*} After 72 h. ^{*h*} After 48 h.

insufficiently low pK_a of **2a**, we then investigated the analogous heterocycle **2b** where the methyl groups had been substituted by trifluoromethyl groups.⁶ This switch was necessary to lower the pK_a sufficiently to allow enolization and hence activation by the amine base; Michael adduct **4b** was formed smoothly and efficiently with DABCO in THF at 30 °C for 96 h. In addition, the diastereoselectivity of this tertiary amine catalyzed process was excellent (>98%; Table 1, entry 2).

Having established a good reactivity profile with 2b and *trans-* β -nitrostyrene, a screen of a small library of cincho-

⁽³⁾ For recent applications of epi-9-amino-9-deoxy cinchona alkaloid derivatives as bifunctional organocatalysts, see: (a) Li, B.; Jiang, L.; Liu, M.; Chen, Y.; Ding, L.; Wu, Y. Synlett 2005, 603. (b) Vakulya, B.; Varga, S.; Csámpai, A.; Šoós, T. Org. Lett. 2005, 7, 1967. (c) McCooey, S. H.; Connon, S. J. Angew. Chem., Int. Ed. 2005, 44, 6367. (d) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. J. Am. Chem. Soc. 2005, 127, 11256. (e) Török, B.; Abid, M.; London, G.; Esquibel, J.; Török, M.; Mhadgut, S. C.; Yan, P.; Prakash, G. K. S. Angew. Chem., Int. Ed. 2005, 44, 3086. (f) Ye, J.; Dixon, D. J.; Hynes, P. S. Chem. Commun. 2005, 4481. (g) Tillman, A. L.; Ye, J.; Dixon, D. J. Chem. Commun. 2006, 1191. (h) Song, J.; Wang, Y.; Deng, L. J. Am. Chem. Soc. 2006, 128, 6048. (i) Wang, Y. Q.; Song, J.; Hong, R.; Li, H.; Deng, L. J. Am. Chem. Soc. **2006**, *128*, 8156. (j) Wang, J.; Li, H.; Zu, L.; Jiang, W.; Xie, H.; Duan, W.; Wang, W. J. Am. Chem. Soc. **2006**, *128*, 12652. (k) Bartoli, G.; Bosco, M.; Carlone, A.; Cavalli, A.; Locatelli, M.; Mazzanti, A.; Ricci, P.; Sambri, L.; Melchiorre, P. Angew. Chem., Int. Ed. 2006, 45, 4966. (1) Bode, C. M.; Ting, A.; Schaus, S. E. Tetrahedron 2006, 62, 11499. (m) Liu, T.; Cui, H.; Long, J.; Li, B.; Wu, Y.; Ding, L.; Chen, Y. J. Am. Chem. Soc. 2007, 129, 1878. (n) Song, J.; Shih, H.; Deng, L. Org. Lett. 2007, 9, 603. (o) McCooey, S. H.; Connon, S. J. Org. Lett. 2007, 4, 599. (p) Wang, B.; Wu, F.; Wang, F.; Liu, X.; Deng, L. J. Am. Chem. Soc. 2007, 129, 768. (q) Chen, W.; Du, W.; Yue, L.; Li, R.; Wu, Y.; Ding, L.; Chen, Y. Org. Biomol. Chem. 2007, 5, 816. (r) Xie, J.; Chen, W.; Li, R.; Zeng, M.; Du, W.; Yue, L.; Chen, Y.; Wu, Y.; Zhu, J.; Deng, J. Angew. Chem., Int. Ed. 2007, 46, 389. (s) Xie, J.; Yue, L.; Chen, W.; Du, W.; Zhu, J.; Deng, J.; Chen, Y. Org. Lett. 2007, 3, 413. (t) Mattson, A. E.; Zuhl, A. M.; Reynolds, T. E.; Scheidt, K. A. J. Am. Chem. Soc. 2006, 128, 3830. (u) Biddle, M. M.; Lin, M.; Scheidt, K. A. J. Am. Chem. Soc. 2007, 129, 3830. For mechanistic studies utilizing the cinchona alkaloids, see: (v) Kumar, A.; Salunkhe, R. V.; Rane, R. A.; Dike, S. Y. Chem. Commun. 1991, 485. (w) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. Angew. Chem., Int. Ed. 2005, 44, 105. (x) Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. J. Am. Chem. Soc. 2006, 128, 13151.

⁽⁵⁾ Coote, S. J.; Davies, S. G.; Middlemass, D.; Naylor, A. J. Chem. Soc., Perkin Trans. 1 1989, 2223.

⁽⁶⁾ Radics, G.; Koksch, B.; El-Kousy, S. M.; Spengler, J.; Burger, K. Synlett 2003, 1826.

nine-derived bifunctional organocatalysts then followed. Other typical reaction parameters such as solvent and temperature were systematically varied and a selection of the findings are detailed in Table 1. Interestingly, catalyst **1c**, which we found to be optimal in enantioselective dimethyl malonate Michael additions^{3f} and Mannich reactions,^{3g} was also found to be optimal in this study. In toluene at 0 °C for 48 h, catalyst **1c** afforded Michael adduct **4b** in 76% ee and >98% de (Table 1, entry 4).

With the optimal conditions established, the scope of the Michael addition reaction was surveyed by initially probing changes to the Michael acceptor. A range of heteroaromatic and aromatic nitro olefins bearing electron-donating or -accepting substituents in the *ortho*, *meta*, and *para* positions were treated with 5-phenyl-1,3-dioxolan-4-one **2b** in toluene at 0 °C in the presence of **1c**. Enantioselectivities ranged from 60% to 89% ee (Table 2). Substituents in the ortho

Table 2. Sc	ope of the	Michael	Addition	Reaction	of $\mathbf{2b}^{a}$
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O Ph	Ľ℃ 2b	$\begin{array}{c} CF_3 & R_{\checkmark} \\ CF_3 & \mathbf{3b}-m \\ \mathbf{1c} \ (0.0) \end{array}$	NO ₂ (0.5 equiv) 05 equiv), 0	► O ₂ °C	O N R	Ph 4c-I);F ₃);F ₃ n
entry		R	solvent	time (h)	yield (%) ^b	de	$ee (\%)^d$
		N	DING	(11)	(70)	(,0)	(,0)
1	4c	o-Br-Ph	PhMe	336	58	>98	89
2	4c	o-Br-Ph	CH_2Cl_2	288	72	>98	79
3	4d	m-Br-Ph	PhMe	30	71	>98	68
4	4e	p-Br-Ph	PhMe	72	59	>98	73
5	4e	p-Br-Ph	$\rm CH_2\rm Cl_2$	48	85	>97	68
6	4f	o-OMe-Ph	PhMe	72	65	>97	74
7	4g	m-OMe-Ph	PhMe	24	50	>97	71
8	4g	m-OMe-Ph	CH_2Cl_2	48	70	>98	68
9	4h	p-OMe-Ph	PhMe	72	81	>97	73
10	4i	m-Me-Ph	PhMe	40	70	>98	69
11	4j	p-Me-Ph	PhMe	40	67	>97	70
12	4k	o-Cl-Ph	PhMe	264	52	>97	82
13	41	2-naphth	PhMe	72	62	>97	75
14	4m	2-furyl	PhMe	24	69	>93	60
15	4n	2-thienyl	PhMe	48	88	>98	66

^{*a*} Reaction was carried out with **2b** (1.0 equiv), **3b**-**n** (0.5 equiv), and **1c** (0.05 equiv) in solvent (1.0 M in **3**). ^{*b*} Isolated yield. ^{*c*} Determined by ¹H NMR. ^{*d*} Determined by HPLC analysis with a chiral column.

position on the ring increased reaction time and gave rise to the highest enantioselectivities (entries 1 and 12, 89% and 82% ee, respectively). Despite conditions being optimal for enantioselectivity, the reaction yields occasionally fell into the 50s when toluene was used as solvent. In such cases, yields could be enhanced by switching to dichloromethane as solvent where only a small decrease in enantioselectivity was observed (Table 2, entries 2, 5, and 8 vs entries 1, 4, and 7, respectively).

Attention then moved to the aryl group of the pronucleophile; three derivatives of **2b**, bearing electrondonating or electron-withdrawing groups in the *para* position of the phenyl ring, 5a-c, were prepared from the parent mandelic acids and hexafluoroacetone. These were subsequently treated with *trans-\beta*-nitrostyrene and catalyst **1c** in dichloromethane at 0 °C. In all three cases the adducts **6a**–**c** were formed in high yield and diastereoselectivity. Reaction rates varied considerably with the fastest belonging to the most electron poor derivative **6a**. Enantioselectivities were moderate to good in all cases (Table 3).

Table 3. Scope with Respect to the Dioxolanone $Pro-nucleophile^a$

$\begin{array}{c} Ar & CF_3 & III & NO_2 \\ Ar & CF_3 & \mathbf{3a} \left(0.5 \text{ equiv} \right) \\ 5a-c & CH_2 Cl_2, 0 ^\circ C \end{array} \xrightarrow{O_2 N} \begin{array}{c} O & CF_3 \\ Ar & Ga-c \end{array}$	$\begin{array}{c} O \\ Ar \\ CF_3 \\ CF_3 \\ 5a-c \end{array}$	Ph NO ₂ 3a (0.5 equiv) 1c (0.05 equiv), CH ₂ Cl ₂ , 0 °C	O ₂ N Ph fa-c
---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------	-------------------------------------------------------------------------------------------------------	-----------------------------

entry		R	time (h)	yield (%) ^b	de (%) ^c	ее (%) ^d
1	6a	$p ext{-} ext{CF}_3 ext{-} ext{Ph}$	2	71	>98	60
2	6b	p-Br-Ph	24	92	>98	60
3	6c	p-OMe-Ph	48	77	>98	70

^{*a*} Reaction was carried out with 5a-c (1.0 equiv), 3a (0.5 equiv), and 1c (0.05 equiv) in CH₂Cl₂ (1.0 M in 3). ^{*b*} Isolated yield. ^{*c*} Determined by ¹H NMR. ^{*d*} Determined by HPLC analysis with a chiral column.

With the scope of the reaction established, the synthetic utility of the Michael adducts was investigated. A selected adduct *rac*-**4b** was synthesized on a gram scale and subjected to routine alcoholysis, hydrolysis, and aminolysis conditions (Scheme 2).

Scheme 2. Reactions Demonstrating the Synthetic Utility of the Michael Adducts and X-ray Structure of (*R*,*R*,*P*)-**11**



Potassium carbonate mediated methanolysis at room temperature gave a quantitative yield of methyl ester 7 whereas treatment with aqueous potassium carbonate solution afforded the α -hydroxy acid 8 in unoptimized 51% yield. Aminolysis with propylamine in dichloromethane afforded the propylamide 9 in quantitative yield after stirring for 15 min at room temperature. A zinc/aqueous hydrochloric acid reduction of the nitro group yielded the γ -lactam **10** in 98% yield.^{4b,7}

In a further aminolysis reaction with (*R*)-1-(4-methoxyphenyl)ethylamine, the absolute and relative stereochemistry of one (**11**) of the two diastereomeric products (**11** + **12**) was unambiguously determined by single-crystal X-ray diffraction as (*R*,*R*,*R*).⁷ In a repeat of this aminolysis reaction with enantioenriched **4b** (76% ee, >98% de) from Table 1, **11** was found to be the major diastereoisomeric product. This result confirmed the preferential addition of the dioxolan-4-one nucleophile to the *Re* face of *trans-β*-nitrostyrene mediated by bifunctional catalyst **1c**, in agreement with our previous studies using dimethyl malonate.^{3f}

In conclusion, racemic 5-aryl-1,3-dioxolan-4-ones have proven effective as pro-nucleophiles in stereoselective Michael addition reactions to nitro olefins catalyzed by bifunctional cinchona alkaloid-derived organocatalysts. The reaction products contain two contiguous stereogenic centers, one of which is a fully substitued carbinol, and are formed with near-perfect diastereocontrol and in good enantiomeric excess. The efficient transformation of the Michael adducts into α -hydroxy acid derivatives has also been demonstrated. Work to expand further the pro-nucleophile pool and to exploit 5-aryl-1,3-dioxolan-4-ones in other addition reactions is underway and will be reported in due course.

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Supporting Information Available: Experimental procedures and spectroscopic data for products 2a,b, 4b-n, 5a-c, 6a-c, and 7-12. This material is available free of charge via the Internet at http://pubs.acs.org.

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⁽⁷⁾ Diastereoisomers **11** and **12** were separated by preparative HPLC with use of an OJ column (see the Supporting Information for details).