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A Catalytic Asymmetric Reaction Involving Enolizable Anhydrides

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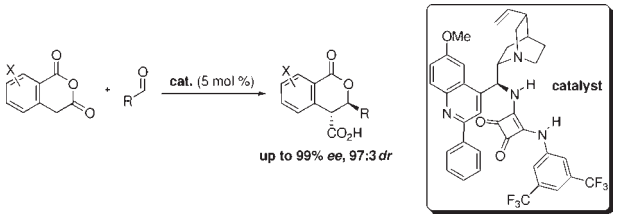
ABSTRACT



In the presence of a highly efficient novel bifunctional organocatalyst at low loadings under mild conditions, enolizable homophthalic anhydrides can be added to a range of aromatic and aliphatic aldehydes to give dihydroisocoumarins, with excellent yields and diastereo- and enantiocontrol (up to 99% *ee*).

Anhydrides have been used as electrophilic acyl transfer agents[1] for over a century.[2] While their chemistry is almost completely dominated by their electrophilicity, the participation of enolizable anhydrides in aldol-like coupling processes has been reported.[3] In 1868, Perkin found that aliphatic anhydrides can condense on heating with aldehydes in the presence of weak carboxylate bases to give α,β-unsaturated acids.[4] Much later, it was shown that cyclic succinic and glutaric anhydrides **1** can undergo formal thermal cycloaddition with either aldehydes[5] or imines[6] to form annulated products of general type **2** (Scheme 1A).[3]

Mechanistically, the two processes are distinct: it is thought that reactions with imines involve the attack of the imine on the anhydride to form an internal acyl ammonium carboxylate ion, which undergoes rate-limiting tautomerization to **3** followed by an *endo-trig* cyclization to yield a lactam product.[3] Aldehydes are not nucleophilic enough to attack the anhydride, and thus these reactions begin with enolization of the anhydride, followed by nucleophilic attack on the aldehyde to generate alkoxide **4**, which then lactonizes to form a dihydroisocoumarin unit in an intramolecular process.[3]

The imine-based methodology has received considerably more attention than the lactone-forming variant,[3] which most often employs homophthalic anhydride (i.e., **5**, R = H, Scheme 1B) and aromatic aldehyde (*i.e.*, **6**) substrates and requires the use of stoichiometric loadings of either a base[7] or a Lewis acid.[8] No catalytic, asymmetric variants of either of these reactions have been reported, despite both the obvious synthetic potential of these products and the relevance of the bicyclic dihydroisocoumarin structural unit in a broad spectrum of chiral natural products possessing a remarkable range of (for example)

(1) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992.
(2) Verley, A.; Bølsing, F. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 3354.
(3) González-López, M.; Shaw, J. T. *Chem. Rev.* **2009**, *109*, 164.
(4) (a) Perkin, W. H. *J. Chem. Soc.* **1868**, *21*, 181. (b) Perkin, W. H. *J. Chem. Soc.* **1877**, *31*, 388.
(5) Jones, J. B.; Pinder, A. R. *J. Chem. Soc.* **1958**, 2612.
(6) (a) Castagnoli, N. *J. Org. Chem.* **1969**, *34*, 3187. (b) Cushman, M.; Gentry, J.; Dekow, F. W. *J. Org. Chem.* **1977**, *42*, 1111. (c) Haimova, M. A.; Mollov, N. M.; Ivanova, S. C.; Dimitrova, A. I.; Ognyanov, V. I. *Tetrahedron* **1977**, *33*, 331.
(7) (a) Bogdanov, M. G.; Palamareva, M. D. *Tetrahedron* **2004**, *60*, 2525. (b) Nozawa, K.; Yamada, M.; Tsuda, Y.; Kawai, K.-I.; Nakajima, S. *Chem. Pharm. Bull.* **1981**, *29*, 3486. (c) Okunaka, R.; Honda, T.; Kondo, M.; Tamura, Y.; Kita, Y. *Chem. Pharm. Bull.* **1991**, *39*, 1298.
(8) (a) Lawlor, J. M.; McNamee, M. B. *Tetrahedron Lett.* **1983**, *24*, 2211. (b) Yu, N.; Poulain, R.; Tartar, A.; Gesquiere, J.-C. *Tetrahedron* **1999**, *55*, 13735.
(9) (a) Wan, S.; Wu, F.; Rech, J. C.; Green, M. E.; Balachandran, R.; Horne, W. S.; Day, B. W.; Floreancig, P. E. *J. Am. Chem. Soc.* **2011**, *133*, 16668. (b) Cichewicz, R. H.; Valeriote, F. A.; Crews, P. *Org. Lett.* **2004**, *6*, 1951. (c) Huang, Y. F.; Li, L.-H.; Tian, L.; Qiao, L.; Hua, H.-M.; Pei, Y.-H. *J. Antibiot.* **2006**, *59*, 355.

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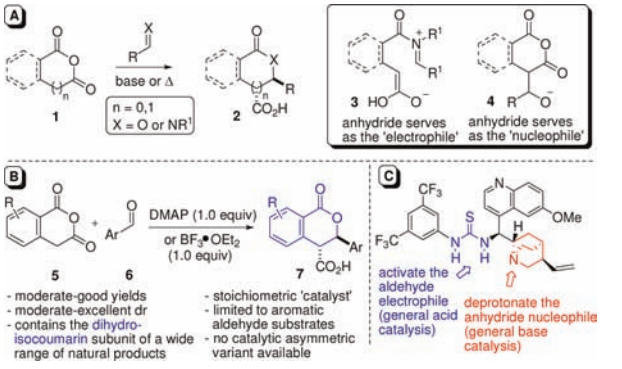
cytotoxic/antiproliferative,[9] phytotoxic,[10] antimicrobial,[11] antifungal,[12] antiulcer,[13] antimalarial,[14] anti-inflammatory,[13] antioxidant,[15] and antiallergic[16] properties.

Our group (among others[17,18]) has recently been engaged in the use of cinchona alkaloid-derived bifunctional organocatalysts[19c,d,20] to promote the asymmetric addition of alcohol[21] and thiol[22] nucleophiles to cyclic anhydrides and related electrophiles.[23] These catalysts rely on the *confluence of relatively weak synergistic catalyst*−*substrate interactions* (mostly the donation of hydrogen bonds to the anhydride and general-base catalysis of the pronucleophile addition).

Since these catalysts are compatible with cyclic anhydride substrates (hitherto only when the anhydrides are being employed as electrophiles) and have been known (in isolated cases) to activate aldehyde/ketone electrophiles,[24] we proposed that, in the absence of a powerful pronucleophile, these bifunctional catalysts could be employed to bring about the activation of an enolizable anhydride as a nucleophile (through catalysis of the equilibrium between it and its enol form), while simultaneously activating the aldehyde through hydrogen bond donation/general acid catalysis (Scheme 1C).

Scheme 1. Annulations of Cyclic Anhydrides with Aldehydes/Imines: Scope and Proposed Strategy



To test this hypothesis, in preliminary experiments we evaluated the addition of homophthalic anhydride (**8**) to benzaldehyde (**9**) in THF at ambient temperature in the presence of a wide range of chiral alkaloid-derived catalysts **11** at 5 mol % loading. In the absence of catalyst, the reaction proceeds very slowly, with moderate diastereoselectivity in favor of ***trans*-10** (Table 1, entry 1). Use of Hünig's base as a catalyst led to considerably faster reactions with no improvement in diastereoselectivity (entry 2). The observed catalysis of this reaction by a non-nucleophilic base lends weight to the hypothesis that the enol of anhydride **8** acts as a nucleophilic species in the reaction. Quinine (**11a**), and its *O*-benzoylated derivative **11b**, promoted the reaction with marginally higher diastereoselectivity. However, the product enantiomeric excesses were inadequate (entries 3−4), as were those obtained from reactions catalyzed by both the C-9 arylated alkaloids **11c** and **11d** (entries 5−6).[22] The bifunctional sulfonamide-substituted catalysts **11e**−**g**, which have proven highly efficacious in the catalysis of asymmetric additions to anhydrides,[18c,f,22b] promoted the formation of predominantly ***trans*-10** in excellent yield, with poor to moderate levels of *ee* (entries 7−9). The exchange of the sulfonamide for urea and thiourea functionality[18] (i.e., catalysts **11h**−**l**) resulted in higher enantioselectivity, with the thiourea-based catalyst **11l** clearly superior to the others (> 75% *ee* for both the *cis* and *trans* diastereomers, with a 9-fold preference for the *trans*-stereoisomer, entries 10−14). The recently developed alkaloid derivative **11m**[24b,c] is a relatively poor catalyst (entry 15). Recently, Rawal[25] introduced a class of squaramide-substituted catalyst as an alternative to (thio)urea-based materials. Squaramide **11n** catalyzed the formation of ***trans*-10** with good diastereoselectivity and 90% *ee* (entry 16). The C_2-symmetric analogue **11o**, which is an excellent catalyst for azlactone alcoholysis,[26] is unsuitable for use in this reaction (entry 17).

(10) Enomoto, M.; Kuwahara, S. *Angew. Chem., Int. Ed.* **2009**, *121*, 1144.

(11) (a) Bogdanov, M. G.; Kandinska, M. I.; Dimitrova, D. B.; Gocheva, B. T.; Palamareva, M. D. *Naturforsch.* **2007**, *62*, 477. (b) Tabopda, T. K.; Fotso, G. W.; Ngoupayo, J.; Mitaine-Offer, A.-C.; Ngadjui, B. T.; Lacaille-Dubois, M.-A. *Planta Med.* **2009**, *75*, 1228.

(12) Hussain, H.; Akhtar, N.; Draeger, S.; Schulz, B.; Pescitelli, G.; Salvadori, P.; Antus, S.; Kurtán, T.; Krohn, K. *Eur. J. Org. Chem.* **2009**, 749.

(13) (a) Shimojima, Y.; Shirai, T.; Baba, T.; Hayashi, H. *J. Med. Chem.* **1985**, *28*, 3. (b) McInerney, B. V.; Taylor, W. C.; Lacey, M. J.; Akhurst, R. J.; Gregson, R. P. *J. Nat. Prod.* **1991**, *54*, 785.

(14) Kongsaeree, P.; Prabpai, S.; Sriubolmas, N.; Vongvein, C.; Wiyakrutta, S. *J. Nat. Prod.* **2003**, *66*, 709.

(15) Nazir, N.; Koul, S.; Quirishi, M. A.; Najar, M. A.; Zargar, M. I. *Eur. J. Med. Chem.* **2011**, *46*, 2415.

(16) Yoshikawa, M.; Uchida, E.; Chatan, N.; Kobayashi, H.; Naitoh, Y.; Okuno, Y.; Matsuda, H.; Yamahara, J.; Murakami, N. *Chem. Pharm. Bull.* **1992**, *40*, 3352.

(17) For seminal work on the highly enantioselective (modified) cinchona-alkaloid-mediated desymmetrizations of *meso*-anhydrides see: (a) Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542. (b) Bolm, C.; Gerlach, A.; Dinter, C. L. *Synlett* **1999**, 195. (c) Bolm, C.; Schiffers, I.; Dinter, C. L.; Gerlach, A. *J. Org. Chem.* **2000**, *65*, 6984.

(18) (a) Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965. (b) Atodiresei, I.; Schiffers, I.; Bolm, C. *Chem. Rev.* **2007**, *107*, 5683. (c) Rodriguez-Docampo, Z.; Connon, S. J. *ChemCatChem* **2012**, *4*, 151. (d) Honjo, T.; Sano, S.; Shiro, M.; Nagao, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 5838. (e) Rho, H. S.; Oh, S. H.; Lee, J. W.; Lee, J. Y.; Chin, J.; Song, C. E. *Chem. Commun.* **2008**, 1208. (f) Oh, S. H.; Rho, H. S.; Lee, J. W.; Lee, J. E.; Youk, S. H.; Chin, J.; Song, C. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 7872.

(19) (a) Li, B. -J.; Jiang, L.; Liu, M.; Chen, Y. -C.; Ding, L. -S.; Wu, Y. *Synlett* **2005**, 603. (b) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967. (c) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (d) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481.

(20) Hiemstra, H.; Marcelli, T. *Synthesis* **2010**, 1229.

(21) Peschiulli, A.; Gun'ko, Y.; Connon, S. J. *J. Org. Chem.* **2008**, *73*, 2454.

(22) (a) Peschiulli, A.; Quigley, C.; Tallon, S.; Gun'ko, Y.; Connon, S. J. *J. Org. Chem.* **2008**, *73*, 6409. (b) Peschiulli, A.; Procuranti, B.; O' Connor, C. J.; Connon, S. J. *Nat. Chem.* **2010**, *2*, 380.

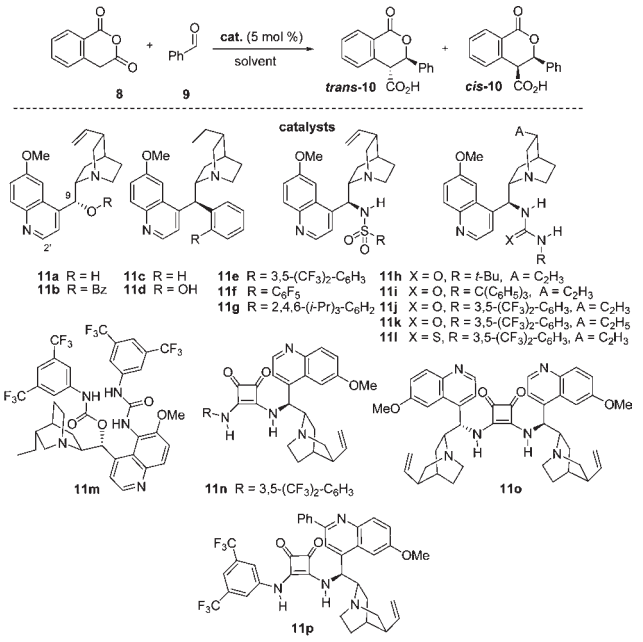
(23) Quigley, C.; Rodriguez-Docampo, Z.; Connon, S. J. *Chem. Commun.* **2012**, *48*, 1443.

(24) (a) Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 929. (b) Palacio, C.; Connon, S. J. *Org. Lett.* **2011**, *13*, 1298. (c) Palacio, C.; Connon, S. J. *Chem. Commun.* **2012**, *48*, 2849.

(25) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416.

(26) Lee, J. W.; Ryu, T. H.; Oh, J. S.; Bae, H. Y.; Jang, H. B.; Song, C. E. *Chem. Commun.* **2009**, 7224.

Table 1. Catalyst Evaluation and Optimization Studies



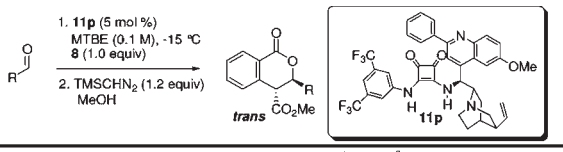
entry	cat.	time (h)	solvent	concn (M)	temp (°C)	yield (%)[a]	*dr*[b] *trans*:*cis*	ee_{trans} (%)[c]	ee_{cis} (%)[c]
1	-	19	THF	0.2	rt	20	75:25	-	-
2	***i*-Pr_2NEt**	19	THF	0.2	rt	95	75:25	-	-
3	**11a**	19	THF	0.2	rt	84	81:19	-7	26
4	**11b**	19	THF	0.2	rt	93	83:17	-28	-1
5	**11c**	19	THF	0.2	rt	99	68:32	1	-3
6	**11d**	19	THF	0.2	rt	93	78:22	-21	-3
7	**11e**	19	THF	0.2	rt	98	90:10	5	30
8	**11f**	19	THF	0.2	rt	97	91:9	-69	35
9	**11g**	19	THF	0.2	rt	98	85:15	-21	24
10	**11h**	19	THF	0.2	rt	96	85:15	72	40
11	**11i**	19	THF	0.2	rt	>99	83:17	58	51
12	**11j**	19	THF	0.2	rt	97	86:14	66	70
13	**11k**	19	THF	0.2	rt	92	85:15	62	68
14	**11l**	19	THF	0.2	rt	92	90:10	79	76
15	**11m**	19	THF	0.2	rt	82	76:24	10	-20
16	**11n**	19	THF	0.2	rt	80	84:16	90	67
17	**11o**	19	THF	0.2	rt	86	78:22	40	32
18	**11p**	24	THF	0.2	rt	96	91:9	93	65
19	**11p**	18	THF	0.1	23	98	91:9	94	73
20	**11p**	18	MTBE	0.1	23	>99	92:8	95	61
21	**11p**	36	CH_2Cl_2	0.1	23	57	82:18	n.d.[d]	n.d.[d]
22	**11p**	18	PhMe	0.1	23	>99	90:10	87	26
23	**11p**	36	MeCN	0.1	23	65	72:28	n.d.[d]	n.d.[d]
24	**11p**	20	THF	0.01	rt	97	82:18	91	92
25	**11p**	36	THF	0.1	0	87	93:7	96	n.d.[d]
26	**11p**	36	MTBE	0.1	0	>99	95:5	96	n.d.[d]
27	**11p**	22	MTBE	0.1	-15	98	96:4	97	n.d.[d]

[a] Determined by ^{1}H NMR spectroscopy using 4-iodoanisole as an internal standard [b] Diastereomeric ratio (400 MHz ^{1}H NMR spectroscopy). [c] Determined by CSP-HPLC, see the SI. [d] Not determined.

Modification of **11n** proved productive: upon installation of a phenyl substituent at C-2′[27] (so that the steric requirement of the quinoline ring is more appropriately balanced around the C-4′−C-9 axis), catalyst performance improved sharply. Use of the novel squaramide **11p** resulted in better yield as well as enantio- and diastereoselectivity (entry 18). Further optimization (entries 19−27) led to the identification of two sets of conditions for the synthesis of ***trans*-10** in ≥98% yield, ≥95:5 *dr*, and ≥96% *ee* at a convenient loading, reaction concentration, and temperature (entries 26 and 27).

(27) Lee, A.; Michrowska, A.; Sulzer-Mosse, S.; List, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 1707.

Table 2. Evaluation of Substrate Scope: Aldehyde Component



entry	product	time (h)	yield (%)[a] of *trans*-diastereomer	*dr*[b]	*ee* (%)[c]
1	***trans*-12**	48	93	97:3	96
2	***trans*-13**	40	93	95:5	95
3	***trans*-14**	48	93	95:5	97
4	***trans*-15**	48	92	93:7	96
5	***trans*-16**	115	78	90:10	91
6	***trans*-17**	48	95	97:3	99
7	***trans*-18**	48	84	94:6	97
8	***trans*-19**	48	90	93:7	98
9	***trans*-20**	22	94[d]	75:25	98 (90)[e]
10[f]	***trans*-21**	93	98[d]	78:22	98 (97)[e]

[a] Isolated yield of the *trans*-diastereomer after column chromatography. [b] Diastereomeric ratio (determined by ^{1}H NMR spectroscopy). [c] Determined by CSP-HPLC, see Supporting Information (SI). [d] Diastereomers inseparable: combined isolated yield. [e] *Ee* of *cis*-isomer in parentheses. [f] At −30 °C.

With a synthetically useful protocol now in hand, our attention turned to the important question of substrate scope (Table 2). The methodology proved robust: when reacted in a 1:1 ratio with anhydride **8**, electron-deficient

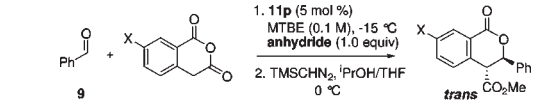
(entries 1–4), electron-rich (entry 5), hindered (entry 6), and heterocyclic aromatic (entries 7 and 8) aldehydes were well tolerated by the catalyst at just 5 mol % loading. Yields and enantiomeric excesses of the isolated *trans*-diastereomers **12**–**19** (to facilitate isolation and separation of the diastereomers, the crude acids were esterified *in situ* after reaction) were generally excellent (≥92% yield and ≥95% *ee* respectively). The deactivated *p*-anisaldehyde proved a greater challenge (entry 5), yet this could still be obtained in good yield and >90% *ee*. Thiophene carbaldehyde also proved a relatively recalcitrant substrate, resulting in an 84% isolated yield (97% *ee*, entry 7) of **18**. Aliphatic aldehydes also undergo the formal cycloaddition; both straight-chain (entry 9) and more hindered 'branched' aldehydes (entry 10) could be converted to **20** and **21** respectively. While the *dr* is uniformly excellent in the case of aromatic aldehydes, the use of aliphatic aldehydes leads to elevated levels of the *cis*-diastereomer. This is mitigated by the fact that the *trans*-diastereomer is formed in both cases in near optical purity; in addition, the *ee* of the formed *cis*-diastereomer is also good to excellent.

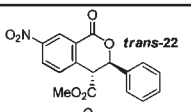
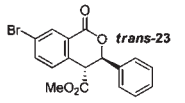
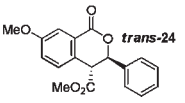
Substitution at the aromatic ring is a feature of several of the medicinally relevant bicyclic dihydroisocoumarin compounds.[9−16] Therefore, we considered it prudent to evaluate the effect of the installation of electron-withdrawing and -donating functionality on the homophthalic anhydride pronucleophile (Table 3).

Deactivating nitro- (entry 1) and bromo- (entry 2) functional groups can be used to form **22** and **23** respectively in excellent *dr* and *ee*. While the yield of the crude acids was excellent in both cases, isolation of these materials is more difficult due to ring opening of the lactones both on esterification and during careful column chromatography to separate the diastereomeric products. Nonetheless, useful yields of pure ***trans*-22** and **23** can be obtained. The electron-donating methoxy group was also found to be compatible (*i.e.*, ***trans*-24**, entry 3). It is interesting to note that the methoxy group would be expected *a priori* to destabilize the enol tautomer of the anhydride substrate (i.e., the putative nucleophile) and thus reduce its equilibrium concentration, while simultaneously (mildly) activating the nearest carbonyl moeity through an −I effect (−OMe σ_m = 0.10). Thus the observation that the methoxy substituted anhydride reacts considerably more slowly than either homophthalic anhydride itself (Tables 1–2) or the nitro/bromo-substituted analogues (Table 3, entries 1–2) would be consistent with the anhydride keto−enol tautomeric equilibrium being a key factor influencing reaction rate in the catalytic process.

(28) Recently, after the preparation of this manuscript, an alternative highly enantioselective organocatalytic methodology for the synthesis of dihydroisocoumarins via the asymmetric bromolactonization of styrene-type carboxylic acids has appeared: Chen, J.; Zhou, L.; Tan, C. K.; Yeung, Y. -Y. *J. Org. Chem.* **2012**, *77*, 999.

Table 3. Substrate Scope: Homophthalic Anhydride Component



entry	product	time (h)	yield (%)[a] of *trans*-diastereomer	*dr*[b]	*ee* (%)[c]
1	 *trans*-22	96	63 (87)[d]	94:6	91
2	 *trans*-23	64	68 (95)[d]	95:5	93
3	 *trans*-24	164	65 (81)[d]	95:5	96

[a] Isolated yield of the *trans*-diastereomer after column chromatography. [b] Diastereomeric ratio (determined by 400 MHz ^{1}H NMR spectroscopy). [c] Determined by CSP-HPLC, see the SI. [d] Yield (determined by ^{1}H NMR spectroscopy using an internal standard) of the *trans*-diastereomer prior to esterification and chromatography in parentheses.

In summary, it has been demonstrated (for the first time in an asymmetric catalysis context) that enolizable anhydrides can be coupled with aldehydes in the presence of a chiral bifunctional organocatalyst to form lactone products. In a process reminiscent of the aldol reaction, it was first demonstrated that homophthalic anhydride could react with benzaldehyde in the presence of a catalytic amine base. This allowed the catalysis of this reaction by a novel bifunctional cinchona alkaloid to generate a dihydroisocoumarin structure with the formation of two new stereocenters in 98% yield, 97% *ee*, and 96:4 *dr* under convenient conditions.[28] The scope of the reaction is robust; electron rich, electron-deficient, hindered, and heterocyclic aromatic aldehydes, in addition to both α-branched and unbranched aliphatic aldehydes are all compatible. Substitution on the anhydride component is also tolerated.

Acknowledgment. Financial support from the European Research Council (ERC) is gratefully acknowledged

Supporting Information Available. Experimental procedures, ^{1}H and ^{13}C NMR spectra, characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.