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Development of a Formal Catalytic Asymmetric [4 + 2] Addition of Ethyl-2,3-butadienoate with Acyclic Enones

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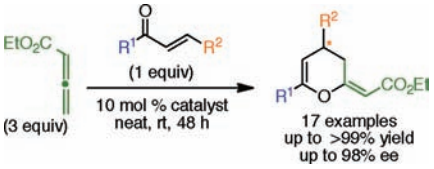
ABSTRACT



Allene esters are unique not only as excellent electrophiles but also because of their ability for subsequent reactivity after the initial nucleophilic attack. A mechanistically inspired cyclization using ethyl-2,3-butadienoate and acyclic enones to provide dihydropyrans in excellent yields and enantioselectivity under solvent-free conditions at room temperature is reported.

The Baylis–Hillman reaction has been extensively studied for its utility to forge C–C bonds catalyzed by N-based Lewis bases such as 1,4-diazabicyclo[2,2,2]octane (DABCO).[1] Recent advancements include the development of catalytic asymmetric variants.[3] The use of allene esters as primary electrophiles for the Baylis–Hillman reaction expands the repertoire of products, as subsequent reactions add to the complexity of the final structures.[3c] In the latter context, the use of chiral N- or P-based Lewis bases has been reported with various secondary electrophiles;[2,4] however development of a reaction with acyclic enones as secondary electrophiles has not been explored.[6] Considering our endeavor in developing synthetic routes to heterocyclic nuclei,[5] our interest was piqued by the possibility of employing acyclic enones as secondary electrophiles toward the preparation of a library of complex dihydropyrans as key intermediates for constructing complex motifs.[7]

Figure 1 illustrates the divergence in products obtained from the reaction of **1** with allenoate **2**, catalyzed with either phosphines[2a] or amines.[2b] Two main factors seem to contribute to the formation of cyclic products in the phosphine catalyzed pathway: (a) the presence of 'd' orbitals on phosphorus that support an expanded valence shell enables the reaction of the transient enolates **6a,c** in the manner depicted to generate ylides **6b,d**; (b) a rapid proton transfer in **6b,d** initiates catalyst turnover. Yet, nitrogen cannot exhibit a similar genre of reactivity, as the lack of 'd' orbitals does not indulge ylide formation under these conditions. Thus, proton transfer leading to the illustrated elimination (Figure 1, **7a,b**), albeit slowly, results in the formation of α-substituted allenes.

(1) (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Baylis, A. B. H., M. E. D. In *German Patent 2* 1972; Vol. *155*. (c) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815.

(2) (a) Du, Y. S.; Lu, X. Y.; Yu, Y. H. *J. Org. Chem.* **2002**, *67*, 8901. (b) Evans, C. A.; Miller, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 12394.

(3) (a) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219. (b) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049. (c) Chen, X. Y.; Wen, M. W.; Ye, S.; Wang, Z. X. *Org. Lett.* **2011**, *13*, 1138.

(4) (a) Cowen, B. J.; Saunders, L. B.; Miller, S. J. *J. Am. Chem. Soc.* **2009**, *131*, 6105. (b) Guan, X. Y.; Wei, Y.; Shi, M. *J. Org. Chem.* **2009**, *74*, 6343. (c) Meng, X. T.; Huang, Y.; Chen, R. Y. *Org. Lett.* **2009**, *11*, 137. (d) Voituriez, A.; Panossian, A.; Fleury-Bregeot, N.; Retailleau, P.; Marinetti, A. *J. Am. Chem. Soc.* **2008**, *130*, 14030. (e) Wallace, D. J.; Sidda, R. L.; Reamer, R. A. *J. Org. Chem.* **2007**, *72*, 1051. (f) Zhao, G. L.; Huang, J. W.; Shi, M. *Org. Lett.* **2003**, *5*, 4737.

(5) (a) Narayan, R. S.; Borhan, B. *J. Org. Chem.* **2006**, *71*, 1416. (b) Schomaker, J. M.; Borhan, B. *J. Am. Chem. Soc.* **2008**, *130*, 12228. (c) Zheng, T.; Narayan, R. S.; Schomaker, J. M.; Borhan, B. *J. Am. Chem. Soc.* **2005**, *127*, 6946.

(6) During the preparation of this manuscript, Tong and coworkers demonstrated the feasibility of this reaction using activated chalcones as secondary electrophiles and benzyl-2,3-butadienoate as a primary electrophile in toluene as a solvent at −30 °C; Wang, X; Fang, T.; Tong, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 5361.

(7) (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (b) Connor, D. T.; Young, P. A.; Strandtmann, M. V. *J. Org. Chem.* **1977**, *42*, 1364. (c) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 911. (d) Gerth, K.; Washausen, P.; Hofle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot.* **1996**, *49*, 71. (e) Hayakawa, H.; Miyashita, M. *Tetrahedron Lett.* **2000**, *41*, 707. (f) Schmidt, B.; Westhus, M. *Tetrahedron* **2000**, *56*, 2421.

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Our venture into the use of acyclic enones was based on the assumption that the increased conformational flexibility of the enolate intermediate could lead to a facile ring closure in preference to the slow proton transfer. As depicted in Figure 2, cyclization of the *hard* oxyanion onto the *hard* enamine, as opposed to that observed with phosphine catalysis (cyclization of the *softer* carbon onto the *softer* vinylphosphonium; see Figure 1), would yield the desired dihydropyran product. Consequently, a variety of enone electrophiles were screened for reactivity with allene ester **2**. Allene ester **8**, incapable of proton transfer, was also chosen to further facilitate the cyclization of **9**. In the event, treatment of acyclic enones (see Table 1) with ethyl-2-methyl-2,3-butadienoate (**8**) in the presence of 20 mol % DABCO provided no product and the secondary electrophile was recovered unreacted. The inertness of **8** in this reaction may be attributed to sterics as a result of the α-methyl group substitution, rendering the intermediate enolate incapable of attacking the secondary electrophile (enone). In contrast, ethyl-2,3-butadienoate (**2**) provided good yields of the *formal* [4 + 2] adducts, albeit via the unanticipated attack of the γ-enolate derived from the activation of **2** with DABCO (Figure 3, enolate **2a**). In fact, previous studies with **2** only report products that arise from α-substitution during the Baylis–Hillman reaction.[2b,4a] Figure 3 illustrates our proposed mechanism leading to the observed products in Table 1, highlighting the γ-substitution of the allene ester (**2a**→**2b**) and subsequent oxygen trap (**2b**→**2c**) to yield the dihydropyran without proton transfer.

Although product **10a**, formed by the γ-attack of the allene predominates, a minor fraction of α-substituted allene product **10b** was observed (Table 1, entry 1). Optimization of reaction conditions revealed that the presence of adventitious water leads to the formation of **10b**. The

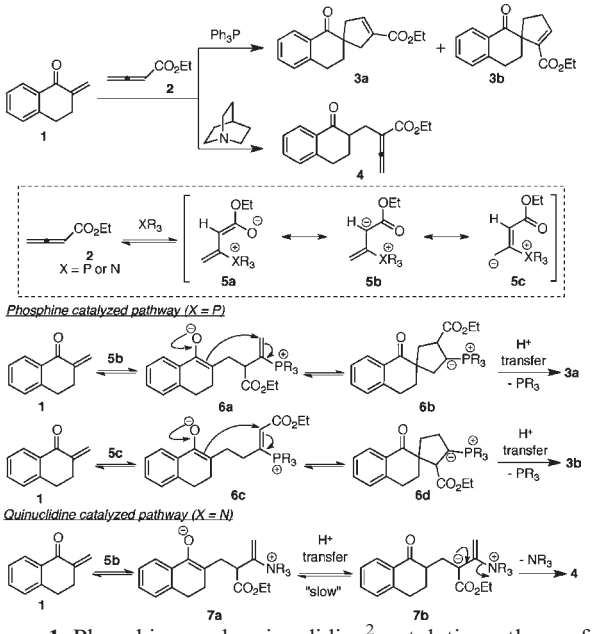


Figure 1. Phosphine and quinuclidine[2] catalytic pathway for allene ester mediated addition reaction.

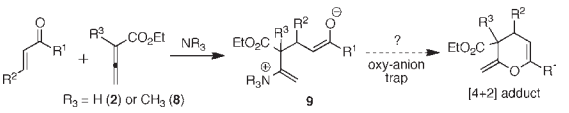


Figure 2. Hypothetical [4 + 2] addition reaction.

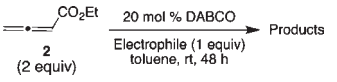
same reaction charged with 4 Å molecular sieves under argon atmosphere yields **10a** exclusively. As shown in Table 1, several secondary electrophiles with varying substitution patterns were employed to investigate the scope of this reaction. Enones **11** and **12** provide the corresponding dihydropyran product as anticipated (Table 1, entries 2 and 3). Dypnone (**13**), a β,β-disubstituted enone (entry 4), did not yield product, presumably indicating the intolerance of the reaction to increased sterics at the β-position of the enone. It is noteworthy that the isolated mass balance of the latter reactions was the unreacted enone. The allene ester **2** does decompose at rt regardless of the absence or presence of the secondary electrophile, an observation that was helpful in further optimization of this reaction, leading to high yields of products as will be described below.

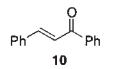
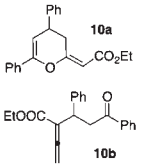
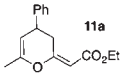
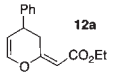
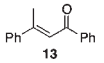
We next explored the possibility of enantiocontrol at C4 by employing cinchona alkaloids (and their derivatives) as chiral amine catalysts for the Baylis–Hillman reaction. Chalcone **10** was chosen as the model substrate in the reaction of **2** as the primary electrophile using 10 mol % of the chiral amine for initial screening efforts; the reactions were performed in toluene at rt. Preliminary results were encouraging since every catalyst that furnished the desired product displayed enantioselectivity, with most surpassing 90% *ee*. Not surprisingly, the monohydrochloride salts of cinchonine (**G**) and cinchonidine (**H**) did not yield product, suggesting that the quinuclidine nitrogen is needed for catalysis.

Although the initial screening delivered the desired products in good enantiomeric excess, the low yields (10–20%) were clearly a problem. Surprisingly, increasing the catalyst loading up to 30 mol % did not make any quantifiable difference in the isolated yields. Hatekeyama's catalyst (**E**), which reportedly enhances the rate of reaction through H-bonding with secondary electrophiles,[3a] marginally improved the yield (30%), although the *ee* suffered in the process (59%). Any attempt to externally activate the secondary electrophile by addition of acidic or basic additives led to faster decomposition of **2**. A screen of different solvents with a large range of polarities was not conclusive, with comparable efficiencies for both polar and nonpolar solvents (see Supporting Information (SI)).

We next resorted to a concentration study, mindful of the tendency for cinchona alkaloids to aggregate at high concentrations (which often leads to deterioration of their catalytic and stereoinductive ability).[8] Gratifyingly, the highest yields were obtained under neat reaction conditions (see SI), providing the products in synthetically useful quantities, and also maintaining high enantiomeric excess. Since, the catalyst and chalcone are both solids, the loading of **2** up to

Table 1. Initial Results for [4 + 2] Addition Reaction



entry	electrophile	products	yields[a]
1	 **10**	 **10a** **10b**	70% (76%)[b] 15%[c]
2	 **11**	 **11a**	55%
3	 **12**	 **12a**	75%
4	 **13**	No Reaction	---

[a] Isolated yields after column chromatography. Due to thermal sensitivity of the products, solvents were removed under vacuum without heating. [b] Reaction was performed in presence of 4 Å MS. [c] Not observed under anhydrous conditions.

3−4 equiv was necessary to provide a reaction medium with efficient mixing.[9] The increased concentration along with the higher equivalence of **2** leads to a faster reaction rate prior to its degradation via nonproductive pathways. It is also noteworthy that no significant deleterious effects result from the self-aggregation of cinchona alkaloids or their derivatives, most probably because stereochemical induction results after the addition of the catalyst to the allenoate (**2**). Aggregation of the zwitterionic intermediate is less likely as compared to the neutral catalyst.

The scope of the reaction was tested with a number of enones as secondary electrophiles, employing the best four catalysts from Figure 4 (Table 2 lists only three catalysts; complete data for all four catalysts are given in the SI). It is evident from the results that electron donation through R^1 does not favor the formation of the transient oxyanion **2b** (Figure 3) and furnishes a low product yield (Table 2, entries 2 and 9). Although, electron-withdrawing R^2 groups gave better yields (entries 4, 5, and 8), the yields are not affected dramatically by electron-donating groups (entries 6, 11, and 16). Aliphatic enones provided the desired products in lower yields (Table 2, entries 13-15); presumably, the slower reaction rate leads to more reactant degradation. Aromatic and heteroaromatic enones were stable under the reaction conditions and furnished excellent yields of the desired products with excellent enantioselectivity.

(8) (a) Rho, H. S.; Oh, S. H.; Lee, J. W.; Lee, J. Y.; Chin, J.; Song, C. E. *Chem. Commun.* **2008**, 1208. (b) Williams, T.; Pitcher, R. G.; Bommer, P.; Gutzwill, J.; Uskokovi, M. *J. Am. Chem. Soc.* **1969**, *91*, 1871.

(9) Ethyl-2,3-butadienoate (**2**) was mostly decomposed after 48 h at rt even when stored under an inert atmosphere. This rate of decomposition was one of the reasons that compelled its use in superstoichiometric amounts.

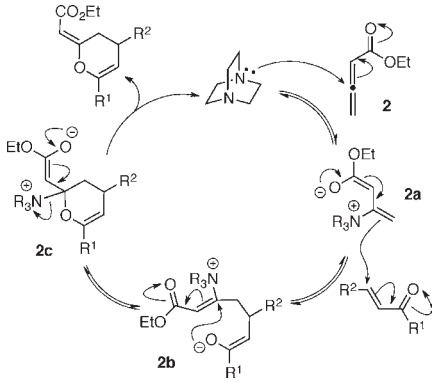


Figure 3. Proposed mechanism for the [4 + 2] addition.

Moreover, we were able to access both enantiomers by a simple switch of the pseudoenantiomeric catalyst. Regardless of electronic and steric factors, the enantioselectivity of the reaction was not greatly influenced by the substitution pattern on R^1 or R^2. Figure 3 depicts a putative mechanism for the formation of the dihydropyran products in Tables 1 and 2. Evidence for this mechanism was obtained from ESI-MS analyses of reaction intermediates (see SI).

To further probe the basis for stereoinduction, an exhaustive DFT calculation at the B3LYP/6-31G* level using toluene as solvent was performed. A large number of possible reaction trajectories (> 20) for the approach of chalcone relative to the adduct of catalyst **B** and **2** were examined (see SI for details). The results revealed that the difference in

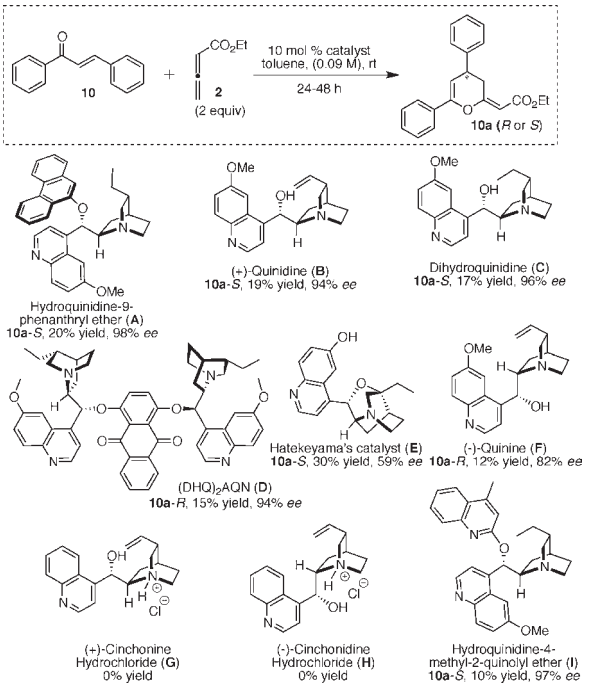
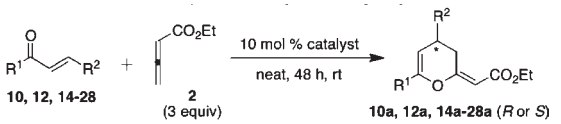


Figure 4. Development of an asymmetric protocol.

Table 2. Substrate Scope of the Asymmetric [4 + 2] Addition Reaction[a]



entry	R^1	R^2	catalyst	product	yield	% ee
1	Ph	Ph	**A**	**10a**-*S*	93%	97
			D	**10a**-*R*	89%	88
2	*p*-OMe-C_6H_4	Ph	**A**	**14a**-*S*	39%	96
			D	**14a**-*R*	42%	82
3	*p*-NO_2-C_6H_4	α-naphthyl	**B**[b]	**15a**-*S*	>99%	97
			D	**15a**-*R*	94%	90
4	Ph	*p*-CN-C_6H_4	**A**	**16a**-*S*	81%	97
			D	**16a**-*R*	55%	89
5	Ph	*p*-Br-C_6H_4	**A**	**17a**-*S*	92%	96[e]
			D	**17a**-*R*	82%	91[e]
6	Ph	*p*-OMe-C_6H_4	**A**	**18a**-*S*	60%	96[e]
			D	**18a**-*R*	52%	83[e]
7	*p*-NO_2-C_6H_4	*p*-OMe-C_6H_4	**A**	**19a**-*S*	58%	95[e]
			D	**19a**-*R*	49%	84[e]
8	*p*-CH_3-C_6H_4	*p*-Cl-*m*-NO_2-C_6H_3	**A**	**20a**-*S*	66%	90[e]
			D	**20a**-*R*	50%	92[e]
9	*p*-MeO-C_6H_4	*p*-Br-C_6H_4	**A**	**21a**-*S*	16%	95
			D	**21a**-*R*	15%	85
10	*o*-MeO-C_6H_4	*p*-F-C_6H_4	**A**	**22a**-*S*	>99%	97[e]
			D	**22a**-*R*	63%	81[e]
11	*o*-Br-C_6H_4	2-furanyl	**A**	**23a**-*S*	61%	96
			D	**23a**-*R*	52%	79
12	*m*-Br-C_6H_4	*p*-Ph-C_6H_4	**A**	**24a**-*S*	98%	98[c]
			D	**24a**-*R*	70%	79
13	CH_3	*n*-C_5H_{11}	**B**[b]	**25a**-*S*	10%	87
			D	**25a**-*R*	11%	77
14	H	Ph	**A**	**12a**-*S*	45%	95
			D	**12a**-*R*	30%	80
15	H	*n*-C_3H_7	**B**[b]	**26a**-*S*	18%	N.D.[d]
			D	**26a**-*R*	12%	N.D.[d]
16	*o*-Cl-C_6H_4	*p*-OMe-C_6H_4	**A**	**27a**-*S*	>99%	97[e]
			D	**27a**-*R*	58%	77[e]
17	*p*-I-C_6H_4	*p*-Br-C_6H_4	**A**	**28a**-*S*	51%	95[e]
			D	**28a**-*R*	36%	87[e]

[a] Ratios were determined by chiral HPLC. [b] Catalyst loading was 20 mol %. [c] Reaction was performed on 1 g scale of **24**. [d] Enantiomers could not be resolved by HPLC analysis. [e] Reactions were performed using **4** equiv of **2**.

energy for the two diastereomeric transition states is 2.5 kcal/mol in favor of the observed (*S*)-enantiomer (Figure 5). This is in excellent agreement with the experimentally observed selectivity of 98:2 *er* (see SI, Table S1, entry 14). The two transition states in Figure 5 orient the reacting molecules such that a close proximity of the counterions (electrostatic stabilization) is achieved. The gauche interaction encountered in **TS2** (highlighted bonds in red, Figure 5) makes this transition state energetically more demanding than the orientation suggested in **TS1**.

The synthetic utility of this transformation is dictated by its ability to access both enantiomers with excellent selectivity and its tolerance to various functional groups under solvent-free conditions at rt. Interestingly, by exploiting the stereocenter and the rigid framework of these molecules one can imagine a plethora of electrophiles reacting at the nucleophilic 'enol ether' in a stereoselective

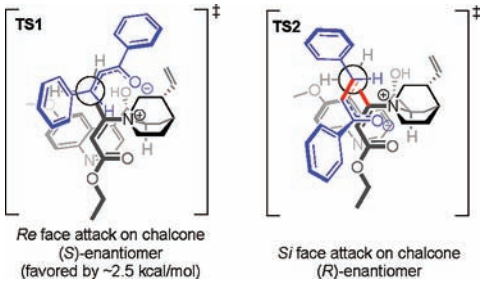
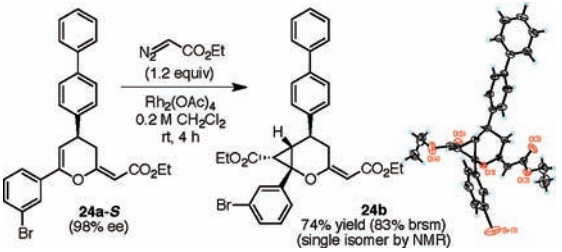


Figure 5. Origin of enantioselectivity (diastereomeric transition states **TS1** and **TS2** determined at B3LYP/6-31G* level). The gauche interactions (highlighted in red bonds) make **TS2** energetically less favored than **TS1**.

Scheme 1. Rh(II) Mediated Cyclopropanation of **24a**-*S*



mode; moreover, upon electrophilic functionalization at C3, the resulting oxacarbenium can undergo attack by nucleophiles, also in a stereoselective manner. As a demonstration of its applicability, $Rh_2(OAc)_4$ mediated cyclopropanation of **24a**-(*S*) provided product **24b** in 74% isolated yield as a single isomer by NMR (Scheme 1). The crystal structure of **24b** provides the absolute stereochemistry of the product, suggesting that the C4 substituent is the stereochemical driver in this reaction.

In summary, we have exploited the difference in phosphine and amine catalysis for the construction of novel dihydropyrans. The employment of cinchona alkaloid catalyzed formal [4 + 2] addition of acyclic enones and allenoate **2** creates an asymmetric center at C4 with efficient stereocontrol, providing a handle for the stereochemical functionalizations of these novel dihydropyrans. The ability to access cyclic products by intermediacy of a *hard* nucleophile unlocks opportunities toward assembly of complex and novel heterocyclic products.

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Supporting Information Available. Experimental procedures and DFT computational data. This material is available free of charge via the Internet at http://pubs.acs.org.