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Organocatalysis

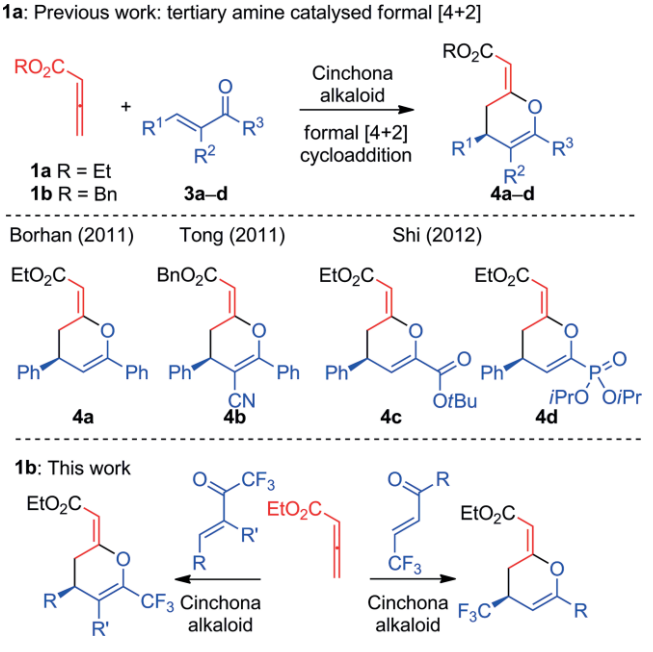
Quinidine-Catalysed Enantioselective Synthesis of 6- and 4-Trifluoromethyl-Substituted Dihydropyrans

Kevin Kasten,[a] David B. Cordes,[a] Alexandra M. Z. Slawin,[a] and Andrew D. Smith*[a]

Abstract: The cinchona alkaloid-catalysed enantioselective formal [4+2] cycloaddition of ethyl 2,3-butadienoate with a range of 1,1,1-trifluoro- and 4,4,4-trifluorobutenones is investigated for the preparation of stereodefined 6- and 4-trifluoromethyl-substituted dihydropyrans. Quinidine proved to be the optimal catalyst, generating the desired products in up to 98 % *ee* and 81 % yield. Stereo- and chemoselective derivatization of the dihydropyrans through hydrogenation is explored.

Introduction

Allenoates are versatile synthetic building blocks that are widely used in the synthesis of carbo- and heterocyclic products.[1] Their simple preparation and commercial availability, combined with their diverse reactivity profile, have made them attractive starting materials that have been utilised within a range of synthetic protocols. When utilised in Lewis base catalysis, addition to the β-carbon of an allenoate generates a zwitterionic intermediate that shows remarkably diverse reactivity with a range of electrophilic coupling partners such as Michael acceptors, dipolarophiles or strained heterocycles. Lewis basic phosphines have been widely explored as catalysts in such processes,[1c,2] while the use of tertiary amine Lewis bases has been relatively less explored and typically show different reaction profiles to phosphines. Within the latter area, Borhan and co-workers first demonstrated the use of cinchona alkaloids to catalyse the formal [4+2] cycloaddition of allenoates and chalcones.[3] For example, quinidine catalysed the reaction of chalcone **3a** (R^1 = R^3 = Ph, R^2 = H) and allenoate **1a** leading to the desired dihydropyran **4a** in 83 % yield and 95 % *ee* (Scheme 1, a). Tong and co-workers extended this protocol through the introduction of a cyano-group in the α-position of the chalcone (**3b**, R^1 = R^3 = Ph, R^2 = CN),[4] generating the corresponding dihydroparan **4b** from allenoate **1b** in 90 % *ee*. Shi and co-workers subsequently utilised α-keto esters **3c** (R^1 = Ph, R^2 = H, R^3 = COO*t*Bu)[5] and α-keto phosphonates **3d** [R^1 = Ph, R^2 = H, R^3 = $P(O)(OiPr)_2$][6] as cycloaddition partners with allenoate **1a** using tertiary amine catalysts, generating dihydropyrans **4c** and **4d** in up to 94 % *ee*. The benefits of incorporating the trifluoromethyl group within target molecules such as increased chemical and metabolic stability, increased lipophilicity, and binding selectivity, are widely recognised and applied in medicinal chemistry.[7] In this context it has previously been demonstrated that 1,1,1-trifluoro- and 4,4,4-trifluorobutenones can act as reactive reaction partners in cinchona alkaloid catalysed processes[8] as well as in isothiourea[9] and NHC-mediated[10] [4+2] cycloaddition processes. Building upon this precedent, in this manuscript the catalytic enantioselective formal [4+2]-cycloaddition of allenoates with regioisomeric 1,1,1-trifluoro- and 4,4,4-trifluorobutenones is demonstrated for the preparation of stereodefined 6- and 4-trifluoromethyl-substituted dihydropyrans (Scheme 1, b). Derivatisation of the products through chemo- and stereoselective hydrogenation is also demonstrated.



Scheme 1. Cinchona alkaloid-catalysed formal [4+2] cycloadditions of allenoates and enones.

[a] *EaStCHEM, School of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife, KY16 9ST, United Kingdom*
E-mail: ads10@st-andrews.ac.uk
http://chemistry.st-andrews.ac.uk/staff/ads/group/index.html

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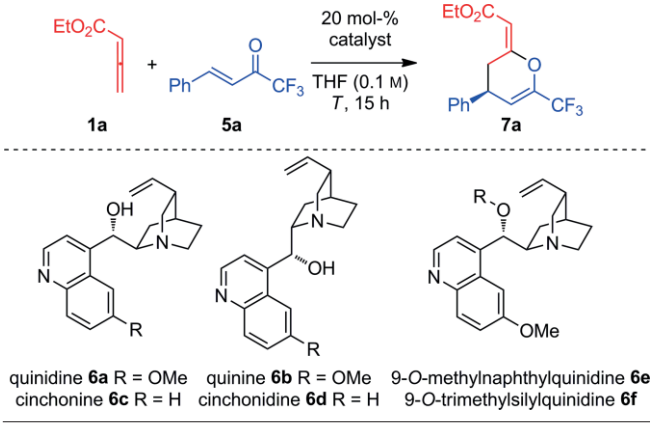
Results and Discussion

Synthesis of 6-(Trifluoromethyl)dihydropyrans – Optimisation:

Initial studies probed the ability of a variety of cinchona alkaloid derivatives as catalysts for the formal [4+2] cycloaddition of allenoates and 1,1,1-trifluorobut-3-en-2-ones. The reaction of ethyl 2,3-butadienoate **1a** and 1,1,1-trifluoro-4-phenylbut-3-en-2-one **5a** to give **7a** was chosen as a model system for reaction optimisation. A range of cinchona alkaloids was screened for catalytic activity and product enantioselectivity (Table 1). Quinidine **6a** and quinine **6b** behaved similarly giving the antipodic products **7a** and **7a(*ent*)** in good yields and promising enantioselectivity (entries 1 and 2, up to 83 % *ee*). Cinchonine **6c** and cinchonidine **6d**, which lack the phenolic methoxy-substituent, showed a significant decrease in product *ee* (entries 3 and 4, both 37 % *ee*). Bulkier 9-*O*-protected quinidine derivatives were also screened; with 9-*O*-methylnaphthyl-quinidine **6e** and 9-*O*-trimethylsilylquinidine **6f** resulted in lower product yield with comparable product enantioselectivities (entries 5 and 6). The effect of temperature on the reaction was also evaluated using quinidine as the catalyst. Notably, a reduction in temperature to 0 °C led to a marginal increase in *ee*, while a substantial loss in product conversion and isolated yield was observed at –78 °C (entries 1, 7 and 8).

Table 1. Catalyst screen.



quinidine **6a** R = OMe
cinchonine **6c** R = H

quinine **6b** R = OMe
cinchonidine **6d** R = H

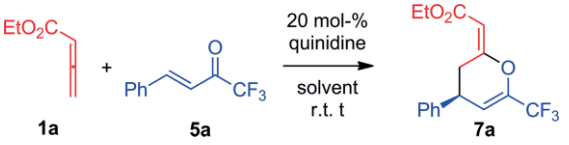
9-*O*-methylnaphthylquinidine **6e**
9-*O*-trimethylsilylquinidine **6f**

Entry	Catalyst[a]	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	**6a**	r.t.	78	76
2	**6b**	r.t.	76	83
3	**6c**	r.t.	64	37
4	**6d**	r.t.	36	37
5	**6e**	r.t.	78	80
6	**6f**	r.t.	36	83
7	**6a**	0	67	81
8	**6a**	–78	16	79

[a] 20 mol-%. [b] Isolated yield. [c] Determined by HPLC analysis against racemic sample.

Due to the recognised influence of the reaction solvent on cinchona alkaloid conformation and therefore product *ee*, an extensive solvent screen of this reaction process was performed.[11] At room temperature polar protic solvents such as methanol and ethanol (Table 2, entries 1 and 2) gave highest enantioselectivity (91 % *ee* and 89 % *ee* respectively), although methanol required extended reaction times and only gave product in 33 % yield. Using 10 or 5 mol-% of quinidine in ethanol the product *ee* remained approximately constant although reduced product conversion and isolated yield were observed (entries 3 and 4). Aprotic polar solvents exhibited an increase in reaction rate with good yields but only moderate enantioselectivity (entries 5–9). The use of ethyl acetate or toluene gave good conversion in short reaction times (maximum 5 h, entries 10–11), although moderate enantio-selectivities were observed. Performing the reaction with water as the solvent gave low selectivity in favour of **7a**(*ent*) (entry 12). In an attempt to further improve the product enantioselectivity and reaction rate, a range of additives was tested in either ethanol or toluene as the solvent (entries 13–15). Marginally improved *ee* was observed when 20 mol-% of benzoic acid, phenol or hexafluoroisopropanol (HFIP) were used in ethanol (95–91 % *ee*), but lower yields were obtained. As a compromise be-

Table 2. Solvent and additive screen for the reaction of **1a** with **5a**.



Entry	Solvent[a]	Additive[b]	*t* [h]	Yield [%][c]	*ee* [%][d]
1	MeOH	–	72	33	91
2	EtOH	–	48	68	89
3[e]	EtOH	–	72	45	88
4[f]	EtOH	–	192	46	90
5	CH_2Cl_2	–	114	82	85
6	acetone	–	47	79	82
7	MeCN	–	21	77	79
8	THF	–	15	78	76
9	Et_2O	–	20	80	75
10	EtOAc	–	5	73	83
11	toluene	–	4	85	79
12	H_2O	–	2	55	18 (*ent*)
13	EtOH	PhCOOH	96	49	95
14	EtOH	HFIP	48	63	93
15	EtOH	PhOH	48	52	91

[a] 0.1 M. [b] 20 mol-%. [c] Isolated yield. [d] Determined by HPLC analysis against racemic sample. [e] 10 mol-% **6a** (QD). [f] 5 mol-% **6a** (QD).

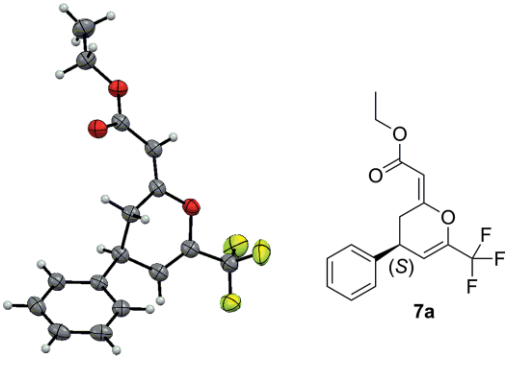


Figure 1. Molecular representation of the X-ray crystallographic analysis of (*S*)-**7a**.

tween product *ee* and yield, as well as reaction rate, ethanol was chosen as the optimum solvent for this transformation.

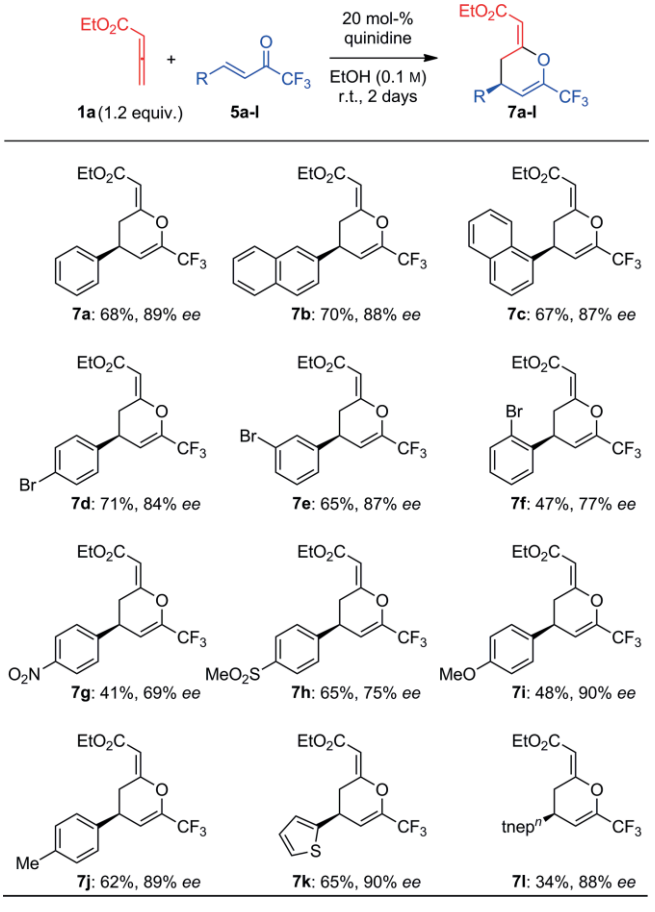
The relative and absolute configuration at C(4) was unambiguously identified to be (*S*)-**7a** through X-ray crystallographic analysis, with the configuration within all subsequent examples assigned by analogy (Figure 1).[12]

Scope and Limitations

I. Using 1,1,1-Trifluorobut-3-en-2-ones as the Reaction Component

Having developed optimum reaction conditions in the model system, the scope of the reaction was probed through variation with the trifluoromethylenone (Table 3). Generally, good yield and high product enantioselectivity were obtained with a range of substituted 4-aromatic and heteroaromatic substituents within the enone. Phenyl-, 1-, and 2-naphthyl-substituents gave essentially identical yields and product *ee* values (**7a**–**7c**). The incorporation of a bromine in the *o*-, *m*- and *p*-position of the phenyl-substituent was tolerated (**7d**–**7f**), although *o*-substitution led to reduced product yield and enantioselectivity.

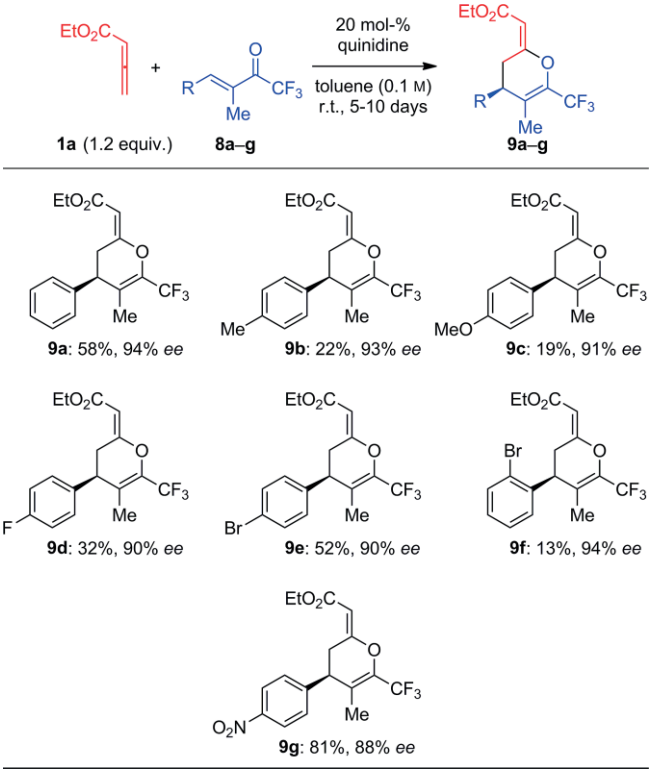
Table 3. Scope for the reaction of **1** with 1,1,1-trifluoromethylbut-3-en-2-ones.



With strongly electron-withdrawing *p*-nitrophenyl- and *p*-mesyl-phenyl substituents lower product *ee* values were observed (**7g**, **7h**), whilst high *ee* but reduced product conversion was obtained with an electron-rich *p*-anisyl- or *p*-tolyl substituent (**7i**, **7j**). Pleasingly, heteroaromatic and aliphatic substituents such as thienyl (**7k**) and pentyl groups (**7l**) were also tolerated, however slow conversion to product, resulting in lower isolated yield, was observed with *n*-pentyl-alkyl substitution (**7l**).

Further studies probed the challenging effect of introducing an α-methyl substituent within the enone moiety (Table 4). Due to a significant decrease in reaction rate in EtOH, toluene was chosen as the reaction solvent, although long reaction times (5–10 d) were required for significant product formation. However, all products **9a**–**9g** were prepared in excellent enantioselectivity. Notable trends indicate that electron-withdrawing *p*-nitrophenyl substituent gave high product conversion and yield (**9g**), whilst a significant decrease in product yield was observed for the *o*-bromophenyl- compared to the *p*-bromo-substituted analogue (**9e** and **9f**).

Table 4. Scope for the reaction of **1a** with 3-methyl-1,1,1-trifluoromethylbut-3-en-2-ones.

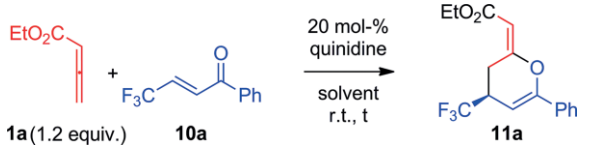


II. Using Isomeric 4,4,4-Trifluorobut-2-en-1-ones as the Reaction Component

Having developed methodology utilising 1,1,1-trifluorobut-3-en-2-ones for the preparation of 6-(trifluoromethyl)dihydropyrans, the use of isomeric 4,4,4-trifluorobut-2-en-1-ones for the preparation of stereodefined 4-trifluoromethyl-substituted dihydropyrans was investigated (Table 5). A brief investigation of the effect of solvent using quinidine **6a** as the catalyst revealed that the reaction proceeded to give the product in good

ee in a range of solvents. Acetone provided the best compromise between high yield and enantioselectivity.

Table 5. Solvent screen for the reaction of **1a** with **10a**.

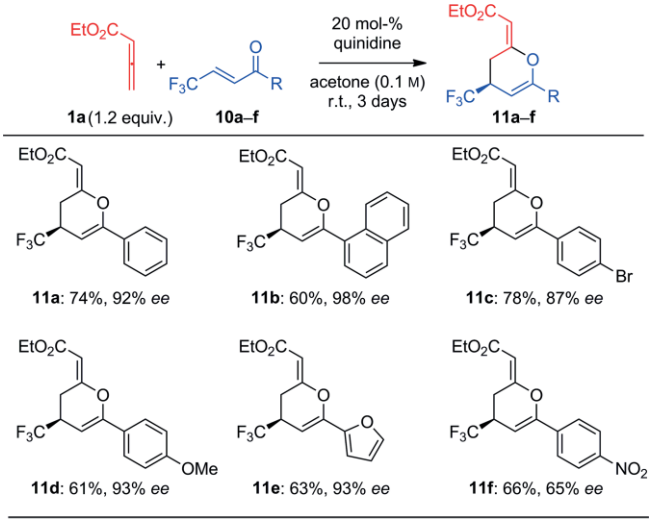


Entry	Solvent[a]	*t* [d]	Yield [%][b]	*ee* [%][c]
1	toluene	1	71	85
2	EtOH	6	21	95
3	THF	2	79	84
4	CH_2Cl_2	6	72	89
5	acetone	2	74	92
6	MeCN	2	80	88
7	AcOEt	4	74	89

[a] 0.1 M. [b] Isolated yields. [c] Determined by chiral HPLC analysis against racemic sample.

Using acetone as the reaction solvent, the generality of this procedure was next examined (Table 6). Good yields and excellent enantioselectivities were generally obtained with aromatic and heteroaromatic substituents (**11a**–**11e**). Only *p*-nitrophenyl substitution exhibited modest enantioselectivity, consistent with the selectivity observed in the isomeric series.

Table 6. Scope for the reaction of **1a** with 4,4,4-trifluoromethylbut-2-en-1-ones.



Consistent with the computational work of Yu et al. we postulate the mechanism of this transformation proceeds via the addition of the tertiary amine Lewis base to the β-position of the allenoate **1a** (Figure 2).[13] The resultant adduct **I** subsequently reacts in an *s-cis* conformation with the enone **5a** with the resultant enolate **II** undergoing cyclisation to give the six-membered ring **III**. Final elimination results in regeneration of the cinchona catalyst and formation of dihydropyran product **7a**.

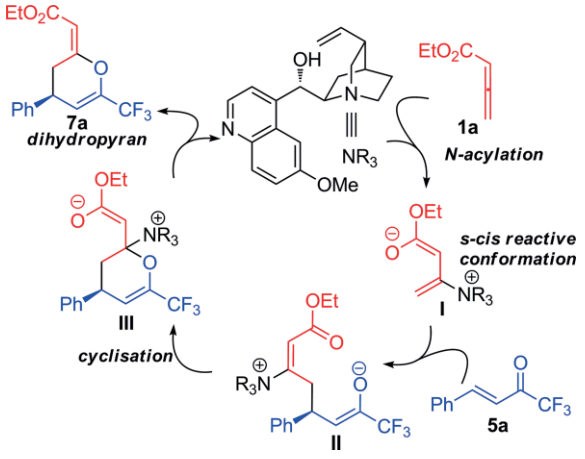
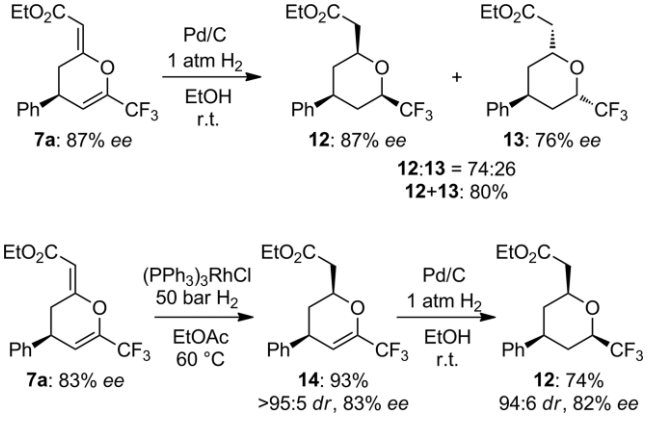


Figure 2. Postulated mechanism for amine catalysed formal [4+2] cycloaddition of allenaotes and enones.

Product Derivatisation

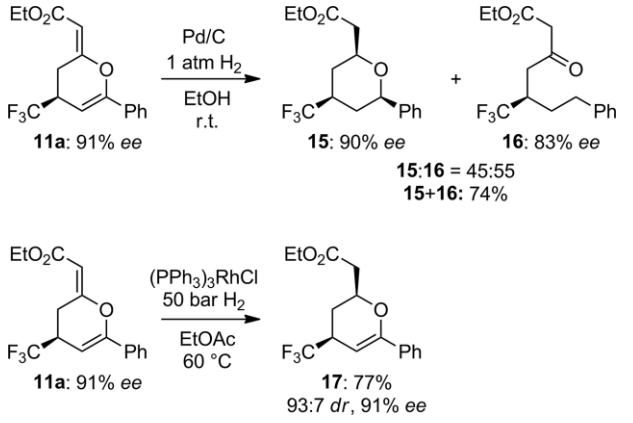
The tetrahydropyran motif is present in many bioactive molecules, such as the *anti*-osteoporotic diospongine, making methods for accessing these architectures highly desirable.[14] To showcase the utility of the methodology developed in this manuscript, derivatisation of **7a** and **11a** to enantioenriched tetrahydropyran scaffolds via hydrogenation was investigated (Scheme 2). Treatment of **7a** (87 % *ee*) with Pd/C and H_2 (1 atm) gave a 74:26 mixture of tetrahydropyran diastereoisomers **12** and **13** in 80 % combined yield. However, hydrogenation of **7a** (83 % *ee*) using Wilkinson's catalyst (50 bar H_2, 60 °C) selectively reduced the exocyclic olefin, giving **14** in 93 % yield and > 95:5 *dr*. Further hydrogenation of **14** with Pd/C gave **12** in > 94:6 *dr* and 74 % yield. The relative configuration within **12**–**15** and **17** was confirmed by nOe and Karplus analyses.[15]



Scheme 2. Selective hydrogenation of dihydropyran **7a** using Pd/C and Wilkinson's catalyst.

The same protocols were applied to dihydropyran **11a**. Using Pd/C as the catalyst a separable 55:45 mixture of tetrahydropyran **15** (> 95:5 *dr*) and ring-opened product **16** in 74 % combined yield.[15,16] The formation of **16** presumably arises from hydrogenation, followed by benzylic hydrogenolysis.[17] However, treating **11a** with Wilkinson's catalyst gave the expected mono-hydrogenated dihydropyran **17** in 77 % yield

and > 95:5 *dr*. Notably **15** and **17** showed no loss of stereointegrity upon hydrogenation, whereas **16** was isolated with slightly diminished *ee* (Scheme 3).



Scheme 3. Selective hydrogenation of dihydropyran **11a** using Pd/C and Wilkinson's catalyst.

Conclusions

To conclude, quinidine promotes the catalytic enantioselective formal [4+2] cycloaddition of allenoates with isomeric 1,1,1-trifluoro- and 4,4,4-trifluorobutenones, allowing the preparation of stereodefined 4- and 6-trifluoromethyl-substituted dihydropyrans with high enantioselectivity. The scope and limitations of these processes has been widely explored giving the corresponding dihydopyrans in moderate to good yield and good to excellent enantioselectivity. The dihydropyran products can be reduced selectively using Pd/C or Wilikinson's catalyst to give the corresponding tetra- and dihydropyrans.

Experimental Section

Example Procedure for the Enantioselective Organocatalytic Generation of Dihydropyrans: To a stirred solution of ethyl 2,3-butadienoate **1a** (0.12 mmol) and the appropriate enone (0.10 mmol) in the appropriate solvent (0.1 M) was added quinidine **6a** (0.02 mmol) at room temperature. After stirring at room temperature the reaction mixture was quenched with ammonium chloride (s) and filtered. The solvent was removed in vacuo and the crude was submitted to column chromatography on silica gel, eluent petroleum ether/CH_2Cl_2 (4:1) unless otherwise stated, to yield the desired dihydropyrans.

Supporting Information (see footnote on the first page of this article): For general experimental details, full characterisation data, NMR spectra and HPLC traces, see the Supporting Information.

Acknowledgments

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Keywords: Organocatalysis · Enantioselective catalysis · Oxygen heterocycles

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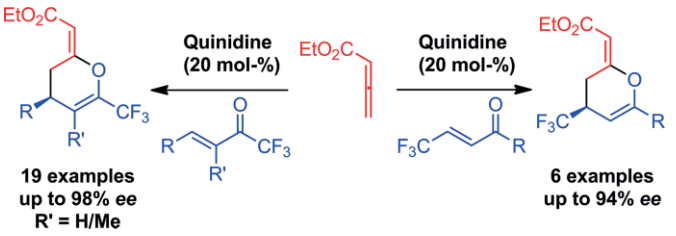
Organocatalysis

*K. Kasten, D. B. Cordes, A. M. Z. Slawin, A. D. Smith** 1–7

Quinidine-Catalysed Enantioselective Synthesis of 6- and 4-Trifluoromethyl-Substituted Dihydropyrans



The quinidine-catalysed enantioselective formal [4+2]-cycloaddition of ethyl 2,3-butadienoate with a range of 1,1,1-trifluoro- and 4,4,4-trifluorobutenones is demonstrated for the preparation of stereodefined C(6) – and 4-trifluoromethyl-substituted dihydropyrans (up to 98 % *ee* and 81 % yield).

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