Asymmetric Synthesis of Tri- and Tetrasubstituted Trifluoromethyl Dihydropyranones from α-Aroyloxyaldehydes *via* NHC-Redox Catalysis

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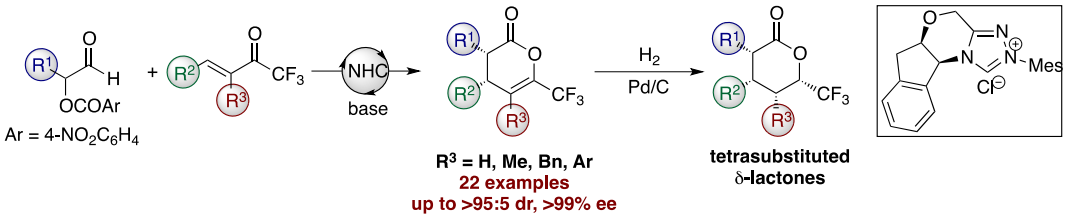
Supporting Information Placeholder

ABSTRACT: The asymmetric synthesis of tri- and tetrasubstituted trifluoromethyl dihydropyranones *via* an NHC-catalyzed redox process, introducing methyl, benzyl and aryl substituents to the *C*(5) position is presented. Their substrate-controlled derivatization into δ-lactones and cyclic hemi-acetals containing stereogenic trifluoromethyl groups is also described.



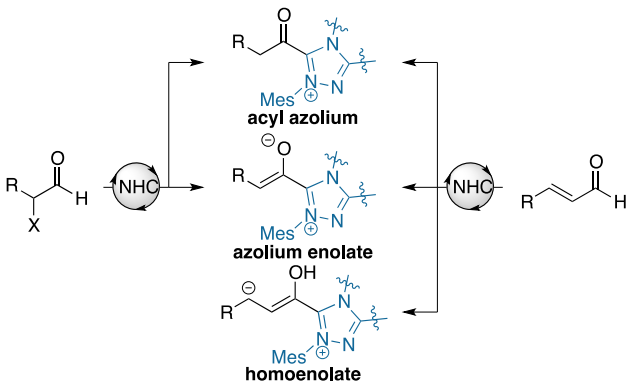
KEYWORDS: asymmetric organocatalysis, N-heterocyclic carbenes, cycloaddition, trifluoromethyl, dihydropyranones, δ-lactones

INTRODUCTION

The asymmetric synthesis of complex molecules containing contiguous stereocenters has been the focus of extensive research owing to the prevalence of such motifs in Nature and the significant challenges in their synthesis.[1] Organocatalysis has become a highly efficient method for the synthesis of these systems,[2] with N-heterocyclic carbenes (NHCs) established as effective organocatalysts for asymmetric transformations.[3] Within this field, NHC-catalyzed redox chemistry allows access to three distinct reactivity modes through which constructive bond-form. Acyl azoliums and azolium enolates can be accessed from α-functionalized aldehydes, while homoenolates, as well as acyl azoliums and azolium enolates, can be utilized from enals (**Scheme 1**).[4]

[4+2] Cycloadditions are a key reaction class within NHC-catalyzed redox azolium enolate chemistry. Currently reported processes utilize [4+2] cycloadditions almost exclusively, with β-substituted α,β-unsaturated ketones, ketimines and aldimines the most common substrates for such reactions.[5,6] To date little work has examined α,β-disubstituted α,β-unsaturated ketones in these processes, which would introduce substituents at the *C*(5) position of the dihydropyranone. The state of the art in this area is represented by work from Kobayashi and Chi, which has been limited to activated *bis*-carbonyl functionalities when preparing *C*(5) substituted dihydropyranones (**Scheme 2**).[7-9]

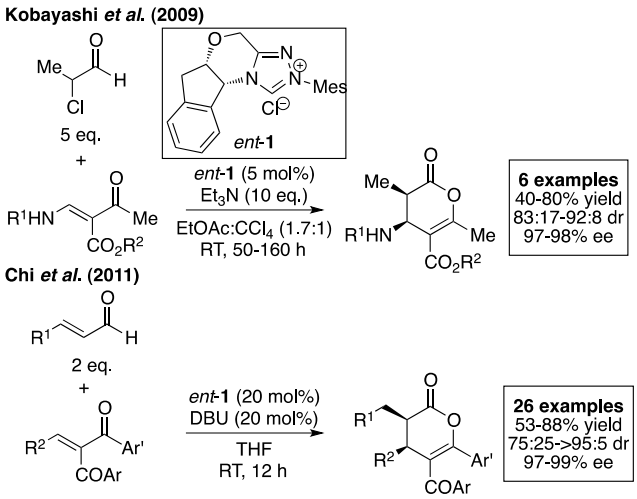
Scheme 1. NHC-redox catalysis mode of reactivity.



We have previously shown that α-aroyloxyaldehydes can act as acyl azolium precursors, allowing the synthesis of both esters and amides in good yield.[10a] Alternatively, these α-aroyloxyaldehydes can be used as azolium enolate precursors, able to undergo formal [4+2] cycloaddition processes with α,β-unsaturated β-trifluoroketones and *N*-aryl-*N*'-aroyldiazines.[10] These aldehydes offer bench-stable alternatives to α-haloaldehydes[5] or α-aryloxyaldehydes[11] and can be synthesized in a single step

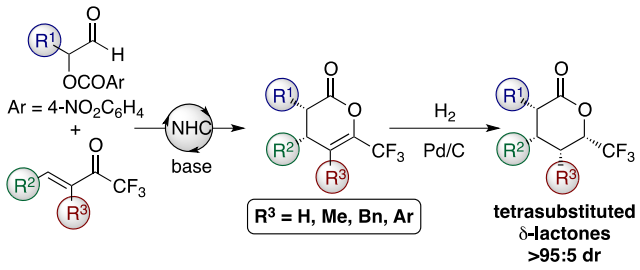
from the corresponding aldehyde using the protocol of Ishihara *et al*.[12]

Scheme 2. Previous work of Kobayashi and Chi in incorporating *C*(5) substituents within dihydropyranones



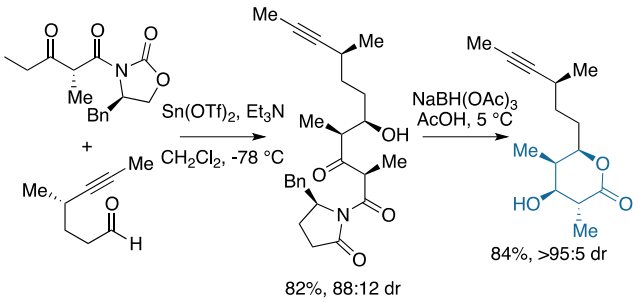
In this manuscript the asymmetric NHC-catalyzed redox [4+2] cycloaddition of α-aroyloxyaldehydes with a range of trifluoromethylenones is reported. This process accommodates variation at both the α- and β-positions within the trifluoromethylenone acceptor, as well as incorporation of the pharmaceutically relevant trifluoromethyl unit (**Scheme 3**).[13,14] This protocol allows methyl, benzyl and aryl substituents to be introduced at the *C*(5) position of the dihydropyranone products through NHC-redox catalysis. The synthetic utility of the dihydropyranones formed has also been shown through their conversion into δ-lactones through substrate controlled stereoselective hydrogenation.

Scheme 3. Expansion of *C*(5) scope and derivatization to highly functionalized δ-lactones.



The δ-lactone motif is a privileged structural class within Nature, appearing within numerous natural products, that exhibit a wide range of biological activity.[15] Many of these δ-lactones contain multiple, contiguous stereocenters, and as such there is great interest in the preparation of such synthetically challenging molecules.[16] The majority of currently reported processes for δ-lactone synthesis rely on the prevalence of *C*(4) hydroxy substituents in δ-lactone-containing natural products. Usual approaches to δ-lactone synthesis tackle the problem in the same way as Nature,[17] namely through an aldol condensation and subsequent lactonization. A common method of approaching this aldol reaction stereoselectively is through the chiral auxiliary chemistry developed by Evans (**Scheme 4**),[18, 19] The method described within this article therefore offers an alternative, catalytic, two-step route towards tetrasubstituted δ-lactones allowing access to unusual substitution patterns that have not been previously accessed.

Scheme 4. Typical δ-lactone synthesis *via* Evans aldol chemistry.[20]

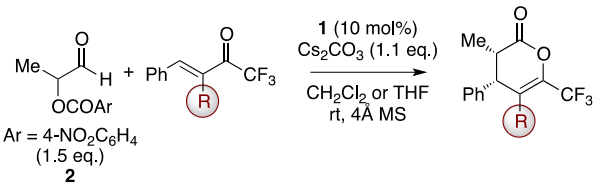


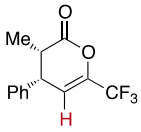
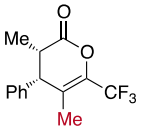
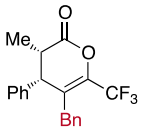
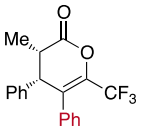
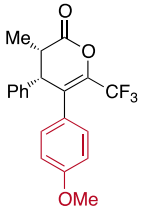
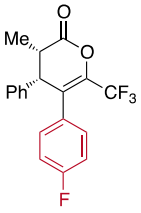
RESULTS AND DISCUSSION

Initial studies probed the effect of the α-substituent on the α,β-unsaturated trifluoromethylketone in a model cycloaddition using α-aroyloxyaldehyde **2**. Synthesis of the α,β-unsaturated trifluoromethylketone was achieved by the protocol of Yuan *et al*.[22] using *N*-phenyltrifluoroacetimidoyl chloride. The α,β-disubstituted α,β-unsaturated trifluoromethylketones were synthesized by an enamine-aldol reaction between a trifluoroketone and a substituted benzaldehyde. Treatment of aminoindanol-derived NHC precatalyst **1** (10 mol%), with cesium carbonate in dichloromethane with 1.5 equivalents of α-aroyloxyaldehyde and 1 equivalent of α,β-unsaturated trifluoromethylketone gave the *syn*-dihydropyranone in 65% yield, >95:5 dr and 99% ee (**Table 1**).

Further investigations varied the α-substituent on the α,β-unsaturated trifluoromethylketone, giving differing substitution at the *C*(5) position of the dihydropyranone. Applying the same conditions to an α-methyl α,β-unsaturated trifluoromethylketone gave 44% conversion into the tetrasubstituted *syn*-dihydropyranone **4** in >95:5 dr. Changing the solvent to THF gave the product in 59% yield, >95:5 dr and >99% ee.[23] With an optimized process for the synthesis of *C*(5) substituted dihydropyranones, investigation of the scope of the α-substituent on the α,β-unsaturated trifluoromethylketone was undertaken. Incorporation of *C*(5) benzyl and phenyl substituents (**5** and **6**), as well as electron-donating and electron-withdrawing aryl substituents (**7** and **8**) proceeded in good to excellent yield, with excellent diastereo- and enantioselectivity throughout (**Table 1**).

Table 1. [4+2] Cycloadditions: α-substituent variation of trifluoromethylenone.

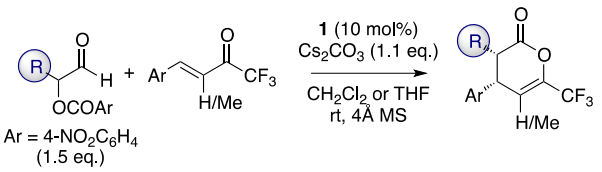


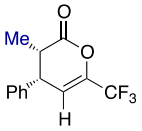
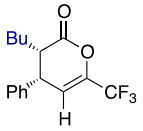
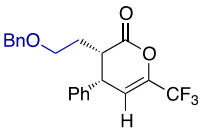
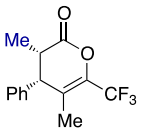
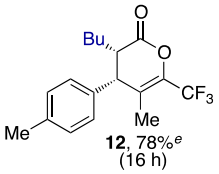
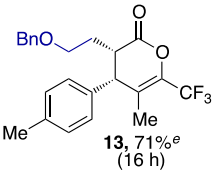
product yield %[a] (time)	dr[b] (ee)[c]	product yield %[a] (time)	dr[b] (ee)[c]
 **3**, 65%[d] (16 h)	>95:5 (99%)	 **4**, 59%[e] (16 h)	>95:5 (>99%)
 **5**, 65%[e] (16 h)	>95:5 (99%)	 **6**, 99%[e] (16 h)	>95:5 (>99%)
 **7**, 80%[e] (16 h)	>95:5 (>99%)	 **8**, 70%[e] (16 h)	95:5 (>99%)

[a]Isolated yield of major diastereoisomer. [b]dr determined by analysis of the crude ^{1}H NMR spectra. [c]ee determined by chiral HPLC or chiral GC analysis. [d]Using CH_2Cl_2. [e]Using THF.

Further work probed variation at the *C*(3) position of the dihydropyranone arising from modification of the α-aroyloxyaldehyde component. A methyl group is readily incorporated (**3** and **11**) as well as an extended alkyl chain (Bu, **9** and **12**) and an alkyl group containing a protected pendant heteroatom (R = CH_2CH_2OBn, **10** and **13**) (**Table 2**). However α-aroyloxyaldehydes containing β-branching (e.g. R = *i*-Pr) are completely unreactive in this system.[24]

Table 2. [4+2] Cycloadditions: α-aroyloxyaldehyde variation.

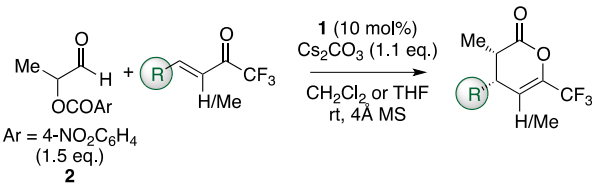


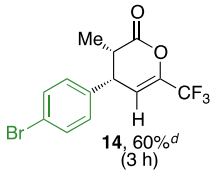
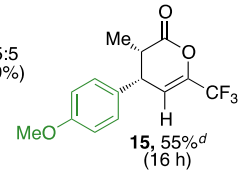
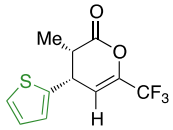
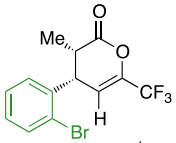
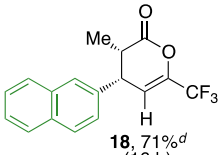
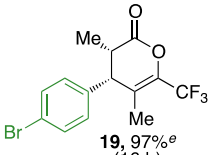
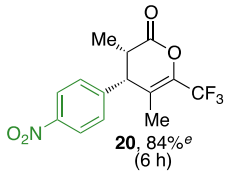
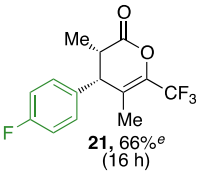
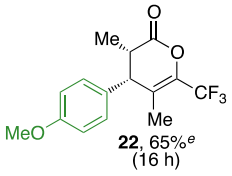
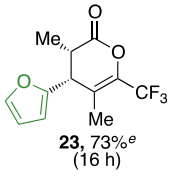
product yield %[a] (time)	dr[b] (ee)[c]	product yield %[a] (time)	dr[b] (ee)[c]
 **3**, 65%[d] (16 h)	>95:5 (99%)	 **9**, 68%[d] (16 h)	>95:5 (99%)
 **10**, 62%[d] (16 h)	94:6 (99%)	 **11**, 58%[e] (16 h)	>95:5 (>99%)
 **12**, 78%[e] (16 h)	>95:5 (>99%)	 **13**, 71%[e] (16 h)	>95:5 (>99%)

[a]Isolated yield of major diastereoisomer. [b]dr determined by analysis of the crude ^{1}H NMR spectra. [c]ee determined by chiral HPLC or chiral GC analysis. [d]Using CH_2Cl_2. [e]Using THF.

Further variation of the β-position of the α,β-unsaturated trifluoromethylketone was investigated. Introducing a *para*-bromophenyl substituent to the *C*(4) position of the dihydropyranone (**14**) allowed for the absolute configuration to be assigned by X-ray crystallography as (3*S*,4*S*).[25] Interestingly this example required a reduced reaction time compared to other substrates, suggesting the electronic nature of the α,β-unsaturated trifluoromethylketone is important in controlling reactivity within this system. Electron-donating aryl groups were also tolerated, as well as heteroaromatic groups, *ortho*-substituted aryl groups and the 2-naphthyl group (**15**-**18**). Exploration of the scope continued using α-methyl α,β-unsaturated trifluoromethylketone, with the introduction of a *para*-bromo substituent (**19**) well tolerated.[23] The electron-withdrawing *para*-nitro group again required reduced reaction times (**20**), and other electron-withdrawing aryl groups (R = *p*-FC_6H_4, **21**) could also be incorporated. Electron-donating aryl groups (R = *p*-$OMeC_6H_4$, **22**; R = *p*-MeC_6H_4, **11**) and heteroaromatic groups (R = 2-furyl, **23**) were tolerated (**Table 3**), however no conversion into the desired product was observed when attempting to introduce an *ortho*-bromo group.

Table 3. [4+2] Cycloadditions: β-substituent variation of the trifluoromethylenone.



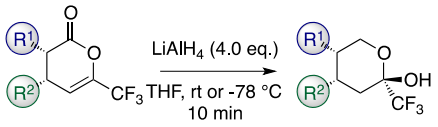
product yield %[a] (time)	dr[b] (ee)[c]	product yield %[a] (time)	dr[b] (ee)[c]
 **14**, 60%[d] (3 h)	>95:5 (>99%)	 **15**, 55%[d] (16 h)	>95:5 (>99%)
 **16**, 58%[d] (16 h)	>95:5 (>99%)	 **17**, 51%[d] (16 h)	>95:5 (99%)
 **18**, 71%[d] (16 h)	>95:5 (97%)	 **19**, 97%[e] (16 h)	>95:5 (>99%)
 **20**, 84%[e] (6 h)	>95:5 (>99%)	 **21**, 66%[e] (16 h)	>95:5 (>99%)
 **22**, 65%[e] (16 h)	>95:5 (>99%)	 **23**, 73%[e] (16 h)	>95:5 (>99%)

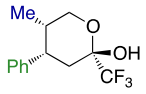
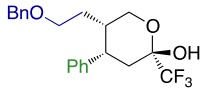
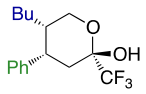
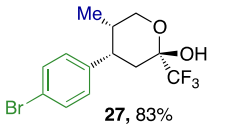
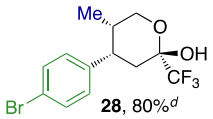
[a]Isolated yield of major diastereoisomer. [b]dr determined by analysis of the crude ^{1}H NMR spectra. [c]ee determined by chiral HPLC or chiral GC analysis. [d]Using CH_2Cl_2. [e]Using THF.

FURTHER FUNCTIONALIZATION: SYNTHESIS OF δ-LACTOLS AND δ-LACTONES

Having successfully synthesized a variety of dihydropyranones, their further transformation into synthetically useful chiral building blocks containing a stereogenic trifluoromethyl group was examined. Treatment of dihydropyranone **3** with lithium aluminium hydride gave the quaternary trifluoromethyl lactol **24** in 81% yield as a single diastereoisomer.[14a] The generality of this process was examined, with incorporation of a variety of *C*(3) substituents (R^1 = CH_2CH_2OBn, **25**; R^1 = Bu, **26**), as well as a *C*(4) electron-rich (R^2 = *p*-$OMeC_6H_4$, **27**) and halogenated (R^2 = *p*-BrC_6H_4, **28**) aryl substituent, with products formed in good yield, excellent dr and ee[25] (**Table 4**).

Table 4. Reduction of dihydropyranones with LiAlH4.

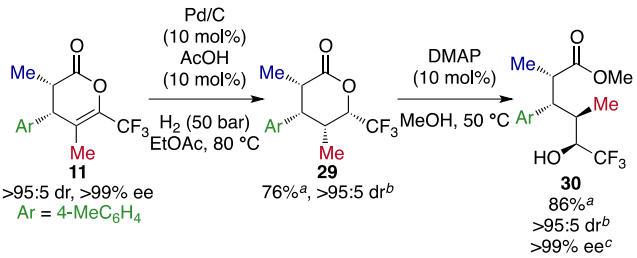


product yield %[a]	dr[b] (ee)[c]	product yield %[a]	dr[b] (ee)[c]
 **24**, 81%	>95:5 (>99%)	 **25**, 76%	>95:5 (98%)
 **26**, 92%	>95:5 (98%)	 **27**, 83%	>95:5 (>99%)
 **28**, 80%[d]	94:6 (>99%)		

[a]Isolated yield of major diastereoisomer. [b]dr determined by analysis of the crude ^{1}H NMR spectra. [c]ee determined by chiral HPLC or chiral GC analysis. [d]Reaction performed at −78 °C.

To access a δ-lactone containing four contiguous stereocenters, hydrogenation of dihydropyranone **11** gave δ-lactone **29** in good yield[23] and as a single diastereoisomer. The relative configuration within **29** was confirmed by NOESY analysis.[23] Ring-opening of δ-lactone **29** through treatment with catalytic DMAP in methanol provided **30** in good yield, >95:5 dr and >99% ee (**Scheme 5**).

Scheme 5. Hydrogenation of dihydropyranone 11 and ring-opening to hydroxyester 30.



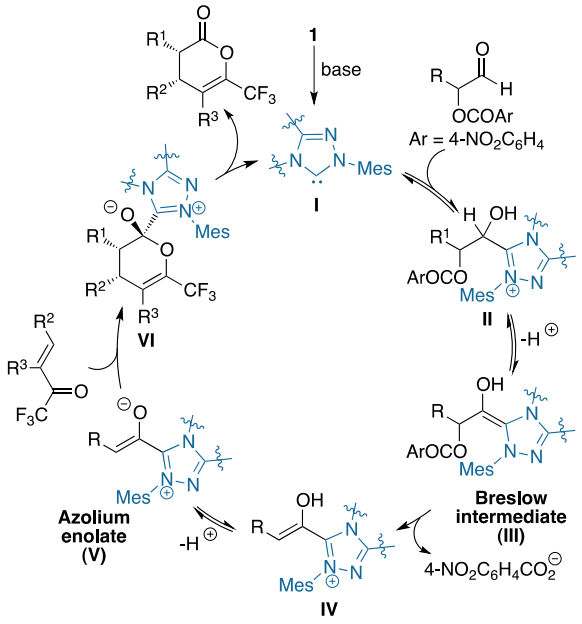
[a]Isolated yield of major diastereoisomer. [b]dr determined by analysis of the crude ^{1}H NMR spectra. [c]ee determined by chiral HPLC or chiral GC analysis.

PROPOSED MECHANISM

The mechanism and stereoselectivity of this NHC-redox process is believed to proceed in a similar manner to that proposed by the groups of Bode and Kozlowski, through a concerted, but highly asynchronous hetero-Diels-Alder

reaction (**Scheme 6**).[26] After deprotonation of triazolium salt pre-catalyst **1**, reversible addition of the free NHC **I** to the aldehyde gives adduct **II**.[27] A deprotonation/reprotonation step allows access to Breslow intermediate **III**, which can eliminate *para*-nitrobenzoate to leave azolium enol **IV**. Deprotonation allows access to the azolium enolate intermediate **V**, which undergoes a concerted, but highly asynchronous, hetero-Diels-Alder [4+2] cycloaddition to leave **VI**.[26] Elimination of the free carbene catalyst completes the catalytic cycle and provides the product.

Scheme 6. Proposed catalytic cycle.



CONCLUSION

In summary, the synthesis of a number of tri- and tetrasubstituted trifluoromethyl dihydropyranones from α,β-unsaturated trifluoromethylketones and α-aroyloxyaldehydes using an NHC-catalysed redox process has been demonstrated, producing synthetically useful products in good yield, diastereoselectivity and enantioselectivity. Stereoselective derivatization of the products under substrate control has also been shown. Current research within this laboratory is focused on developing alternative novel asymmetric processes using α-aroyloxyaldehydes in NHC-redox catalysis.

ASSOCIATED CONTENT

Full experimental procedures and characterization, as well as ^{1}H and ^{13}C NMR spectra for novel compounds and crystallographic data where relevant can be found in the supporting information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(25) Crystallographic data for **14**, **19**, and **28** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 984035, CCDC 984036 and CCDC 984037 respectively.

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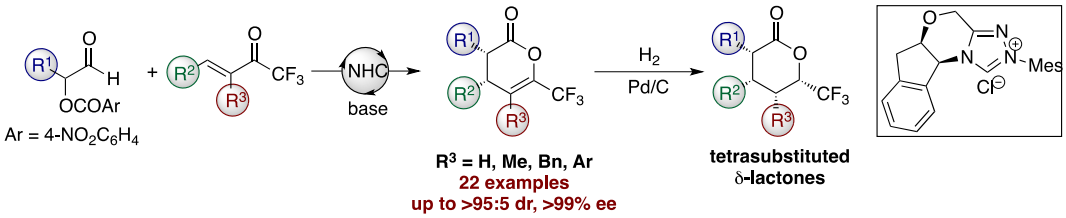

R³ = H, Me, Bn, Ar
22 examples
up to >95:5 dr, >99% ee

tetrasubstituted δ-lactones