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# Expeditious access to *cis*-β-aryl, γ-alkyl disubstituted (±)-γ-butyrolactones *via* nickel-hydride catalysis†

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The 1,4-reduction of β- and γ-substituted butenolides using 5 mol% of $NiCl_2 \cdot 6H_2O$ and $NaBH_4$ in MeOH for rapid access to *cis*-β,γ-disubstituted γ-butyrolactones is described. The reaction was selective for *cis*-products, which were obtained in good to excellent yields. This study showcased the influence of steric hindrance and angle strain on the diastereoselectivity outcome of conjugate reductions facilitated by *in situ* generated nickel-hydride.

The γ-butyrolactone moiety is ubiquitous in natural products such as phaseolinic acid[1a] and in FDA-approved drugs such as pilocarpine, which is used for the treatment of glaucoma, and spironolactone, used for the treatment of high blood pressure and heart failure (Fig. 1). γ-Butyrolactone is a key motif in the structure of an experimental drug[1b] and can serve as a useful synthetic intermediate.[1c,d]

Ring-opening polymerisation (ROP) of cyclic esters has been used to synthesise degradable and chemically recyclable polyesters.[1e] Prior research has demonstrated the importance of γ-butyrolactone (**1**) as a highly desirable building block for the construction of poly(γ-butyrolactone).[1f] Despite some progress, the polymerisation of **1** is challenging due to the low ring strain in the 5-membered ring which has a negative change in enthalpy value that is too small to overcome the large negative entropy change associated with ROP.[1g] To solve this problem, the ring strain of **1** can be increased through the introduction of a substituent at any position on the lactone ring (Fig. 2).

This should enable easier incorporation of γ-butyrolactone units into polymer chains. For example, α-acetyl-γ-butyrolactone (**2**) displayed improved reactivity and displayed huge potential as a monomer in ROP.[1h] However, this potential and the applicability of γ-butyrolactones **2** and **3** as monomers in ROP could be restricted due to the multistep synthetic routes needed for their construction. Hence, this work provides a convenient, economical, and facile access to *cis*-disubstituted γ-butyrolactone of type **3**, that could be explored as a monomer in ROP to produce functional and biodegradable polyesters. In the past decade, metal-hydrides[2] such as Fe–H[3a] and Cu–H[3b] have been exploited for the hydrocarbonation of alkenes. In recent years, Ni–H has demonstrated the potential to functionalise alkenes with a directing group such as boronic esters[4a] and aryl groups[4b,c] next to the alkenyl moiety or remote olefins.[4d,e]

Synthesis of *cis*-(±)-disubstituted γ-butyrolactone has been achieved previously *via* linear precursors. For example, the direct annulation of enals (of type **4**) and aldehydes (of type **5**) was utilised for the stereoselective synthesis of disubstituted (±)-**7**, catalysed by N-heterocyclic carbene **6** (Scheme 1A).[5a] However, this synthetic method furnished all γ-butyrolactones with moderate diastereoselectivities (≤8/1; *cis*/*trans*). Recently, a report described a $B(C_6F_5)_3$-catalysed reduction and lactonisation of γ-keto acids (±)-**8** for the construction of γ-butyrolactone (±)-**10** (Scheme 1B).[5b] The scope of the study was limited to substitutions such as Me, Ph (±)-**8**, allyl, or the propargyl group at the α-position of the ketone, although their

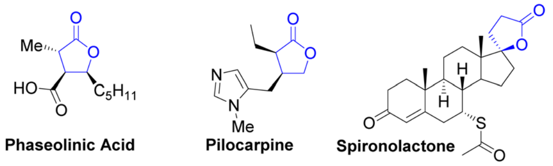

**Fig. 1** γ-Butyrolactone moiety in natural products and medicinal drugs.

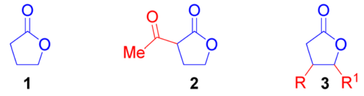

**Fig. 2** γ-Butyrolactones for ring opening polymerisation.

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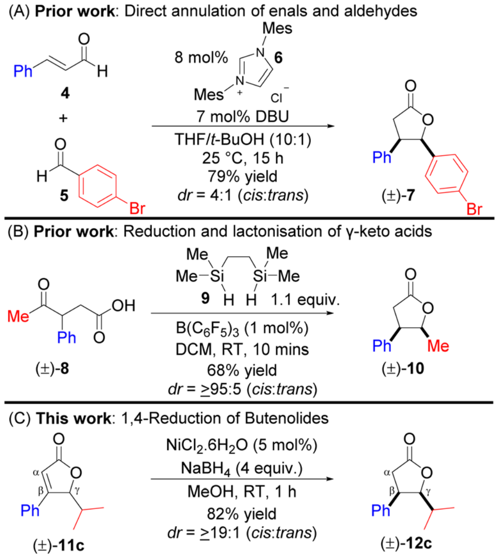


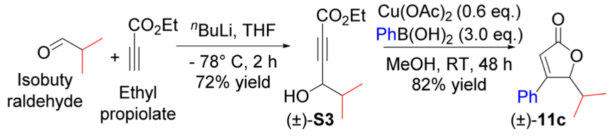
**Scheme 1** Construction of monocyclic *cis*-β,γ-disubstituted (±)-γ-butyrolactones.

corresponding γ-butyrolactones were obtained with excellent *cis* diastereoselectivity. Notably, four synthetic steps will be required to construct keto-acid (±)-**8**,[5c] and most importantly, different starting precursors will be needed for the synthesis of keto acid (±)-**8** derivatives. As a subsequent study to our previous work,[5d] we herein described a convenient, economical, and straightforward access to *cis*-β(aryl),γ(alkyl)-disubstituted (±)-γ-butyrolactones of type **12c** *via* nickel-hydride 1,4-reduction of β,γ-disubstituted α,β-unsaturated lactones of type **11c** (Scheme 1C).[6a–c]

All the β,γ-disubstituted α,β-unsaturated lactones (butenolides) investigated (22 examples) in this study were obtained in two easy steps, starting from the cheap and commercially available ethyl propiolate and the corresponding aldehydes (Scheme 2). For example, the treatment of ethyl propiolate with $^n$BuLi and subsequent addition of isobutyraldehyde provided (±)-**S3**. The two-step one-pot protocol of copper-catalysed conjugate addition of phenyl boronic acid and subsequent *in situ* cyclisation generated butenolide (±)-**11c** from (±)-**S3**.[6d–e] Initial attempts focused on the development of a strategy for the direct synthesis of γ-butyrolactone (±)-**12c** from alkynoate (±)-**S3** *via* nickel-catalysed hydroarylation, cyclisation and then 1,4-reduction using Ni(II) salts such as $Ni(OAc)_2·4H_2O$ and $NiCl_2·6H_2O$ instead of $Cu(OAc)_2$. After 48 h, $NaBH_4$ was added to the reaction; however, (±)-**12c** was obtained in a relatively low yield (<10%), with (±)-**S3** mostly recovered. Based on this observation and in conjunction with previous reports,[7a] it seems that nickel-catalysed hydroarylation of alkynes proceed well when the alkyne bears a phenyl group rather than an ester group at the terminus end.[7b] Subsequent studies (Table 1) were designed and carried out with the aim of understanding the role of each reagent and to propose a plausible reaction mechanism. The starting material was recovered when the reaction was carried out in the absence of $NiCl_2·6H_2O$, and when $NaBH_4$ was replaced with silanes as the hydride source (Table 1, entries 1–4).[7c] The order of addition of the reagents was critical to the feasibility of this reaction (Table 1, entries 5 *vs.* 6).

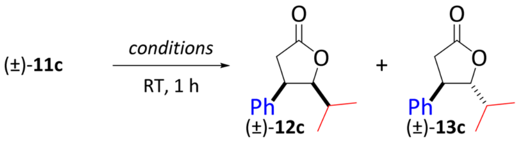
Compound (±)-**12c** was generated diastereoselectively in excellent yield when $NaBH_4$ was added to a stirring light-green mixture of (±)-**11c** and $NiCl_2·6H_2O$. In contrast, the addition of (±)-**11c** to the stirring black suspension of pre-mixed $NiCl_2·6H_2O$ and $NaBH_4$ gave no product.[8a] This nullifies the notion that nickel boride facilitates the 1,4-reduction of the butenolide. The importance of a protic solvent towards the feasibility of the reaction was also noted (Table 1, entry 5 *vs.* entries 7 and 8). A higher mol% of nickel in the reaction resulted in improved yields (Table 1, entries 9 and 10).

The summary of the results in Table 1 postulates a butenolide ligated nickel hydride complex **B** (Scheme 3), since $NiCl_2·6H_2O$, $NaBH_4$ and MeOH worked in tandem.[8b,4c] This ligation enabled the inner-sphere delivery of the hydride, followed by protonation of the Nickel enolate species **D** or **D′** (Fig. 3), thereby generating the *cis* product in a highly diastereoselective manner.[9]



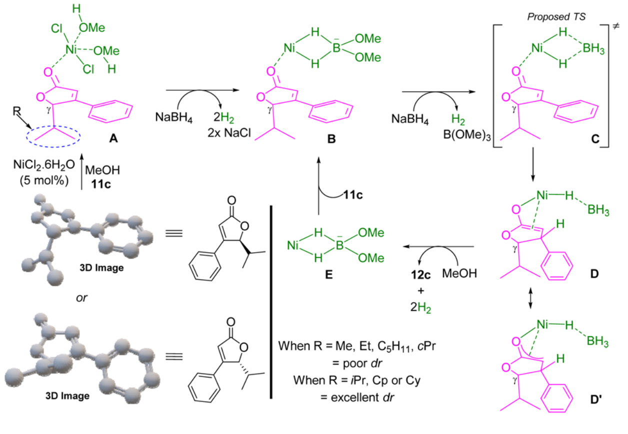
**Scheme 2** Two-step synthesis of (±)-**11c**.

**Table 1** Comprehension of the role of reagents[a]



| Entry | Conditions | 12 : 13 [b] | Yield [c] |
|---|---|---|---|
| 1 | $NaBH_4$, MeOH | — | — |
| 2 | $NiCl_2·6H_2O$ (5 mol%) PMHS (4 eq.), MeOH | — | — |
| 3 | $NiCl_2·6H_2O$ (5 mol%) $PhSiH_3$(4 eq.), MeOH | — | — |
| 4 | $NiCl^2·6H_2O$ (5 mol%) $PhMe_2SiH$ (4 eq.), MeOH | — | — |
| **5** | **$NiCl_2·6H_2O$ (5 mol%) $NaBH_4$(4 eq.), MeOH** | **≥19 : 1** | **82** |
| 6[d] | $NiCl_2·6H_2O$ (5 mol%) $NaBH_4$(4 eq.), MeOH | — | — |
| 7 | $NiCl_2·6H_2O$ (5 mol%) $NaBH_4$(4 eq.), THF | — | — |
| 8 | $NiCl_2·6H_2O$ (5 mol%) $NaBH_4$ (4 eq.), PhMe | — | — |
| 9 | $NiCl_2·6H_2O$ (10 mol%) $NaBH_4$(4 eq.), MeOH | ≥19 : 1 | 88 |
| 10 | $NiCl_2·6H_2O$ (15 mol%) $NaBH_4$(4 eq.), MeOH | ≥19 : 1 | 91 |

[a] Reactions were carried out at the 0.75 mmol scale. [b] Determined by $^1H$ NMR analysis of the crude sample. [c] Isolated yield based on three reaction runs. [d] Formation of nickel boride by stirring $NiCl_2·6H_2O$ and $NaBH_4$ in MeOH for 5 min. After effervescence subsided, a black precipitate was formed, after which (±)-**11c** was added. $Ni(OAc)_2·4H_2O$ also performed well in this reaction.



Scheme 3 Plausible mechanism. See Fig. S4† for more details.

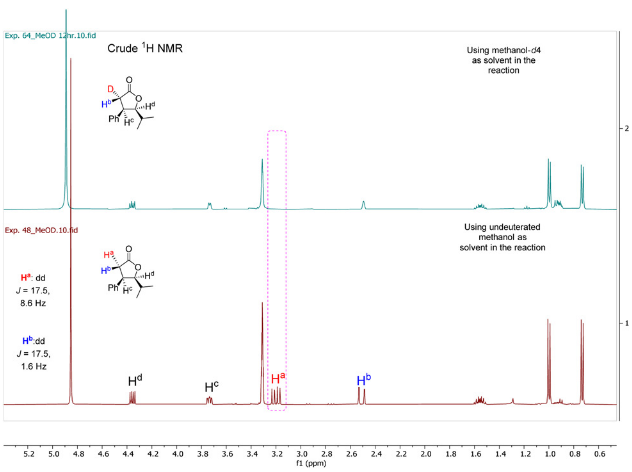
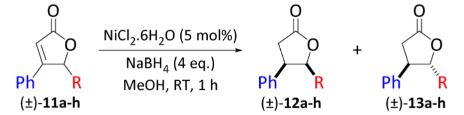


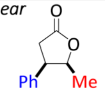
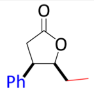
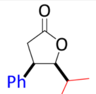
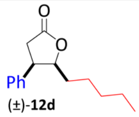
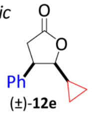
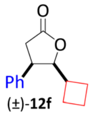
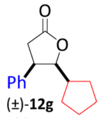
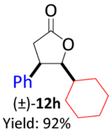
Fig. 3 $CH_3OH$ *vs.* $CD_3OD$ as solvent.

The proposed mechanism in Scheme 3 was experimentally validated by investigating linear alkyl (Me, Et, iPr, and $C_5H_{11}$) substituents at the γ-position (Table 2). While **12a**, **b**, and **d** were furnished in 3 : 1 dr, **12c** was generated as the sole product. This observation can be attributed to the steric hindrance caused by the alteration of the tetrahedral angle.[8d] In addition, we ascertained the correlation between steric hindrance and high diastereoselectivity by exploring cyclic rings at the γ-position (Table 2, **12e–h**). As the flexibility of the ring increases with increasing size (decrease in transannular strain), this allows for conformations that can disrupt the nickel-hydride species, forcing the delivery of the hydride from either the re-face or the si-face but not both.

The impact of angle strain of the γ-substituents on diastereoselectivity is noticeable when the dr of **12c** is compared to that of **12e** and/or **12f**.[8e] Table 3 displays γ-butyrolactones with different aryl substitutions at the β-position. The results showed that their diastereoselectivities were solely dependent on the type of alkyl substituents at the γ-position (*e.g.*, **12i** *vs.* **12o** or **12p** *vs.* **12t**) and they all followed similar trends as shown in Table 2. Next, we explored a buteno-

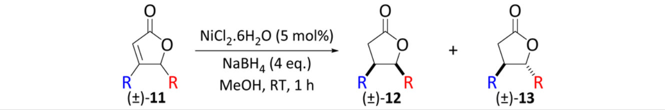
Table 2 Linear and cyclic (R) substituents at the γ-position[a]

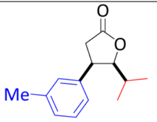
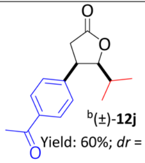
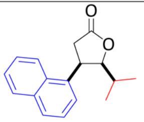
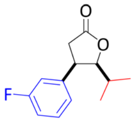
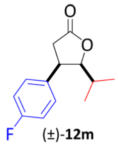
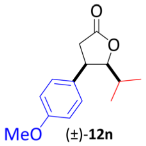
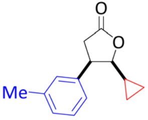
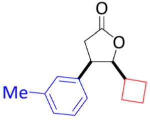
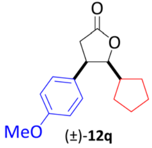
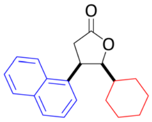
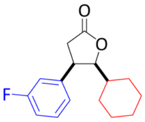
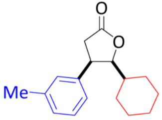
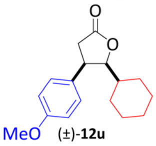
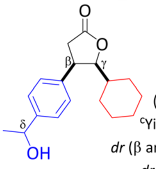


| | | | | |
|---|---|---|---|---|
| *Linear* | <br>**(±)-12a**<br>Yield: 60%<br>*dr* = 3:1 | <br>**(±)-12b**<br>Yield: 62%<br>*dr* = 3:1 | <br>**(±)-12c**<br>Yield: 82%<br>*dr* = ≥19:1 | <br>**(±)-12d**<br>Yield: 61%<br>*dr* = 3:1 |
| *Cyclic* | <br>**(±)-12e**<br>Yield: 60%<br>*dr* = 3:1 | <br>**(±)-12f**<br>Yield: 78%<br>*dr* = 10:1 | <br>**(±)-12g**<br>Yield: 87%<br>*dr* = ≥19:1 | <br>**(±)-12h**<br>Yield: 92%<br>*dr* = ≥19:1 |

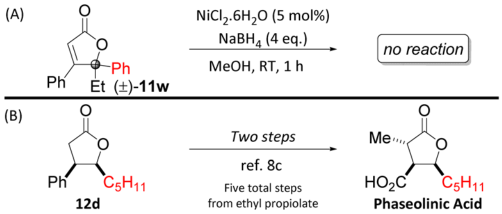
[a] Reaction conditions: (±)-**11a–h** (0.75 mmol), $NiCl_2 \cdot 6H_2O$ (0.0375 mmol), $NaBH_4$ (3.00 mmol, 4.0 eq.), MeOH (10 mL), RT, 1 h. dr values were determined by $^1H$ NMR analysis of the crude sample. Yields are those of the isolated *cis*-products **12a–h**.

Table 3 Scope of study – substituted aryl (R) at the β-position[a]



| | | |
|---|---|---|
| <br>(±)-**12i**<br>Yield: 88%; *dr* = ≥19:1 | <br>[b](±)-**12j**<br>Yield: 60%; *dr* = ≥19:1 | <br>(±)-**12k**<br>Yield: 92%; *dr* = ≥19:1 |
| <br>(±)-**12l**<br>Yield: 91%; *dr* = ≥19:1 | <br>(±)-**12m**<br>Yield: 94%; *dr* = ≥19:1 | <br>(±)-**12n**<br>Yield: 95%; *dr* = ≥19:1 |
| <br>(±)-**12o**<br>Yield: 62%; *dr* = 3:1 | <br>(±)-**12p**<br>Yield: 63%; *dr* = 10:1 | <br>(±)-**12q**<br>Yield: 89%; *dr* = ≥19:1 |
| <br>(±)-**12r**<br>Yield: 97%; *dr* = ≥19:1 | <br>(±)-**12s**<br>Yield: 95%; *dr* = ≥19:1 | <br>(±)-**12t**<br>Yield: 93%; *dr* = ≥19:1 |
| <br>(±)-**12u**<br>Yield: 96%; *dr* = ≥19:1 | <br>(±)-**12v**<br>[c]Yield: 44%<br>*dr* (β and γ) = ≥19:1<br>*dr* (δ) = 1:1 | |

[a] Reaction conditions: as described in Table 2. [b] Using 1.0 eq. of $NaBH_4$ (0.75 mmol). [c] Isolated yield of one of the diastereoisomers.



**Scheme 4** (A) Effect of additional substituent at the γ-position and (B) synthetic utility of γ-butyrolactone **12d**.

lide with a ketone functional group that is susceptible to $NaBH_4$ to test our Ni–H hypothesis. Using 4.0 equivalents of $NaBH_4$, we obtained **12v**. Noteworthily, using 1.0 equivalent of $NaBH_4$, **12j** was produced predominantly in a moderate yield and with excellent dr, accompanied by ketone reduction products (1 : 1).

Previously, we established that $NaBH_4$ alone cannot facilitate the 1,4-reduction of butenolides (Table 1, entry 1). Perhaps, the 1,4-reduction was facilitated by Ni–H catalysis. The lack of reactivity of compound **11w** (Scheme 4A) demonstrated that an additional substituent at the γ-position possibly disrupted the Ni–H species (as shown in B and C, R = Et, Scheme 3), presumably hindering the delivery of the hydride. The relative stereochemistry of the γ-butyrolactones was assigned *cis* based on the observed NOESY spectra (for **12c**, **12g** and **12h**) and the trend in the $^3J_{H-H}$ coupling constant between the key protons on the lactone at the β- and γ-positions (see Fig. S5†). The synthetic utility of this class of *cis*-disubstituted γ-butyrolactone has been shown previously.[8c] **12d** was converted into a biologically active natural product, phaseolinic acid, in two steps.

## Conclusions

Our previous study[2d] described a Cu–H catalysed 1,4-reduction of β-substituted butenolides. Herein, we demonstrated the 1,4-reduction of β- and γ-substituted butenolides *via* Ni–H catalysis, which generated *cis*-disubstituted γ-butyrolactones. This study revealed that γ-butyrolactones with iPr, or cyclopentane or cyclohexane at the γ-position can be obtained in excellent diastereoselectivities and yields.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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## References

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