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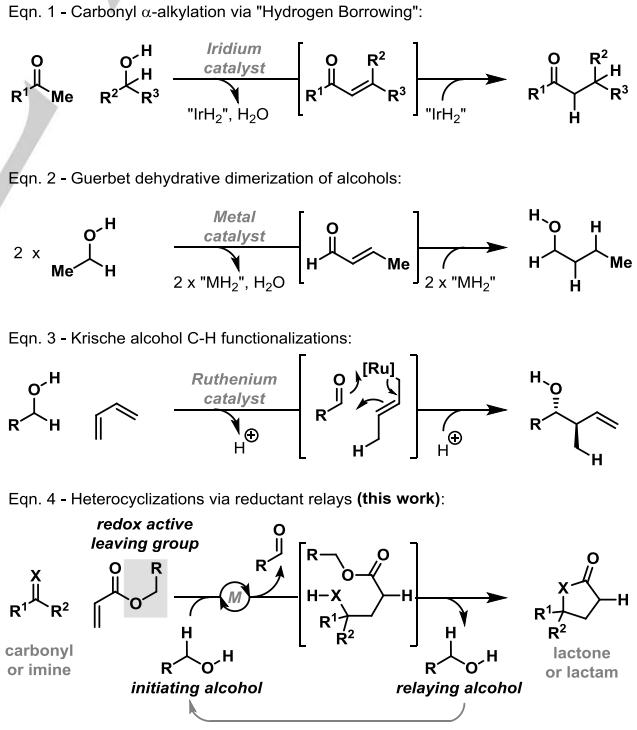
Reductive Coupling of Acrylates with Ketones and Ketimines via a Nickel-Catalyzed Transfer Hydrogenative Reductant Relay Strategy

Craig S. Buxton, David C. Blakemore, and John F. Bower*

Abstract: Ni-catalyzed coupling of benzyl acrylates with activated ketones or imines provides γ-butyrolactones and lactams. The benzyl alcohol byproduct released during the lactonization/lactamization event is relayed to the next cycle where it serves as the reductant for C-C bond formation. This strategy represents a conceptually unique approach to transfer hydrogenative C-C bond formation, providing examples of reductive heterocyclizations where hydrogen embedded within an alcohol leaving group facilitates turnover.

The identification of catalytic paradigms for the direct and atom economical assembly of C-C bonds is a key goal of organic chemistry. Within this context, transfer hydrogenative C-C bond formation has emerged as a powerful platform for reaction design. For example, "hydrogen borrowing" allows the direct α-alkylation of carbonyl compounds with alcohols, via a catalytic dehydrogenation-condensation-reduction sequence (Scheme 1, Eqn. 1).[1] The related Guerbet reaction effects the dehydrative union of two alcohols, providing an efficient method to upgrade bioethanol to butanol (Eqn. 2).[2] Krische and co-workers have pioneered transfer hydrogenative alcohol C-H functionalizations, as exemplified by processes where alcohol dehydrogenation drives the reductive generation of nucleophilic metal-allyls in advance of carbonyl addition (Eqn. 3).[3] Each of these reaction classes merges redox events with C-C bond formation, thus avoiding stepwise generation of reactive functionality and enhancing substantially atom economy. As such, new transfer hydrogenative C-C bond forming strategies are likely to find wide utility in reaction design.

Our studies in this area were initiated by considering synthetic entries to γ-butyrolactones and lactams,[4-7] which are versatile intermediates as well as core motifs in an array of natural products. An appealing, yet unrealized approach to these compounds resides in metal-catalyzed reductive coupling of a carbonyl or imine with an acrylate to afford a γ-amino or -hydroxy ester, which upon cyclization would provide the target (Scheme 1, Eqn. 4). This disconnection requires the identification of a strategy that enables reductive C-C bond formation, but avoids non-productive reduction of the starting materials. We reasoned that these criteria might be fulfilled by coupling the release of the reductant to the formation of the lactone or lactam, thereby minimizing non-productive background reduction events. Such a proposition appears practically challenging, however, a simple solution is availed by harnessing the native reducing power of the alcohol released upon cyclization to drive turnover. In this way, the alcohol byproduct from one cycle is relayed to the next, where it then serves as the reductant for C-C bond formation. Herein, as proof-of-concept, we show that lactones or lactams can be generated by Ni-catalyzed union of activated ketones or ketimines with O-benzyl acrylates. This provides unique examples of reductive heterocyclizations where hydrogen embedded within an alcohol leaving group facilitates catalytic turnover,[8] adding a new vista to the wider area of transfer hydrogenative C-C bond formation.[1-3]



Scheme 1. Transfer hydrogenative C-C bond forming strategies.

In early studies, we assayed a wide range of late transition metal systems for the reductive coupling of isatin **1a** and ethyl acrylate **2a** (R = Et) (Table 1). At 150 °C in PhMe, and with 10

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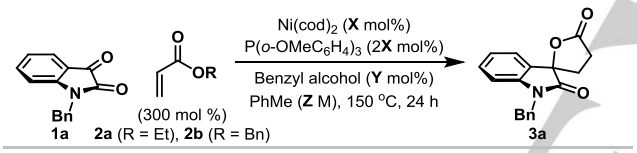
mol% benzyl alcohol as the initiator (see Scheme 1, Eqn 4.), the combination of 7.5 mol% $Ni(cod)_2$ and 15 mol% $P(o\text{-}OMeC_6H_4)_3$ provided target lactone **3a** in 19% yield, with unreacted starting material accounting for the mass balance (Entry 1). Here, according to our reaction design, ethanol released during the first turnover must then function as the reductant for subsequent cycles. Based on this we considered whether more easily oxidized alcohol-based leaving groups might provide increased efficiencies.[9] Ultimately, this led to the conditions outlined in Entry 3, which use 300 mol% benzyl acrylate **2b** (R = Bn) as the reaction partner, and generate **3a** in 84% yield. Some turnover was observed in the absence of the initiating alcohol (Entry 4), likely facilitated by hydrolytic release of BnOH from benzyl acrylate under the reaction conditions. This generates acrylic acid as a byproduct, a component that control experiments found to be inhibitory to the reductive lactonization process.[10] Lower loadings of either the benzyl alcohol initiator or the Ni-pre-catalyst resulted in diminished efficiencies (Entry 5), and use of stoichiometric BnOH also resulted in a lower yield (Entry 6); this latter result highlights the benefits of coupling reductant release to turnover. **3a** was generated in 58% yield when the reaction was run with only 100 mol% **2b** (Entry 7). A Ni(0)-pre-catalyst is essential for efficient reactivity; Ni(II)-systems (e.g. Entry 8) or commonly employed transfer hydrogenation catalysts, such as $[IrCp^*Cl_2]_2$ (Entry 9), were completely ineffective.[11]

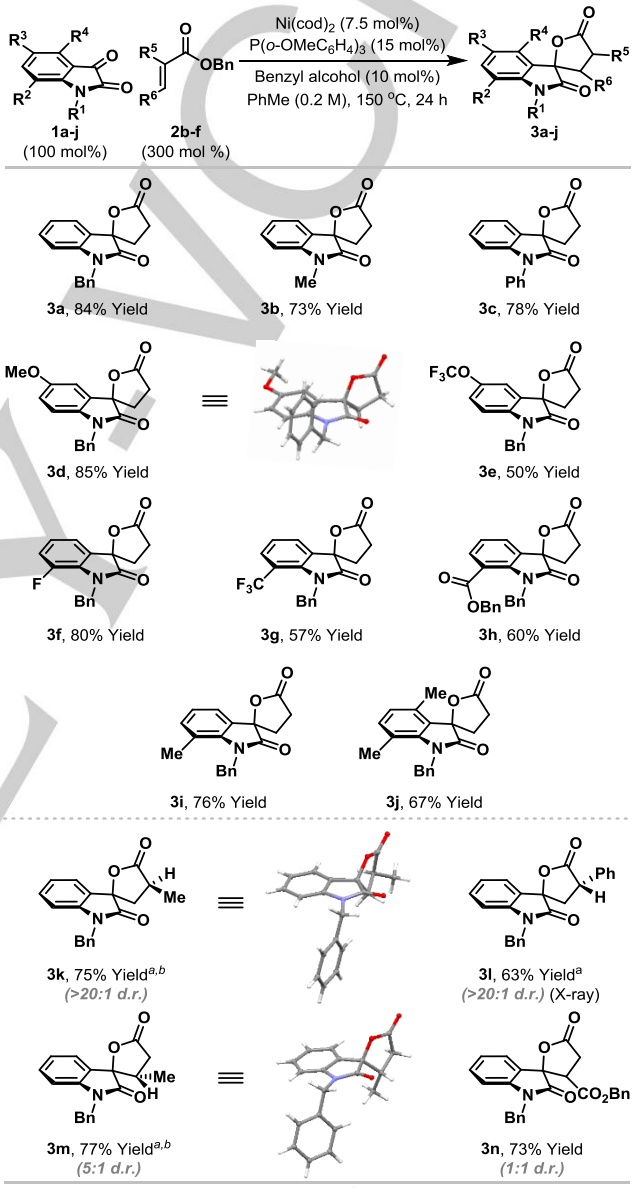


Entry	R	Pre-catalyst	X	Y	Z	Yield[a]
1	Et	$Ni(cod)_2$	7.5	10	0.05	19%
2	Bn	$Ni(cod)_2$	7.5	10	0.05	76%
3	Bn	$Ni(cod)_2$	7.5	10	0.2	84%
4	Bn	$Ni(cod)_2$	7.5	0	0.05	17%
5	Bn	$Ni(cod)_2$	5	5	0.05	38%
6	Bn	$Ni(cod)_2$	7.5	100	0.2	52%
7[b]	Bn	$Ni(cod)_2$	7.5	10	0.2	58%
8	Bn	$NiCl_2$	7.5	10	0.2	<5%
9	Bn	$[IrCp^*Cl_2]_2$	3.75	10	0.2	<5%

[a] In situ yield determined by ^1H NMR analysis vs. 1,4-dinitrobenzene. [b] Using 100 mol% benzyl acrylate **2b**.

Table 1. Preliminary results and optimization studies.

The scope of the process with respect to the isatin component is outlined in Table 2. A variety of electronically distinct systems **1a-j** participated to provide the target spirocyclic systems **3a-j** in moderate to excellent yield. The protocol shows useful functional group tolerance, with both esters (**3h**) and methoxy (**3d**) substituents surviving despite the established lability of these functionalities under Ni(0)-catalyzed conditions.[12] Processes involving disubstituted acrylates required the addition of $Mg(OTf)_2$ as a Lewis acidic co-catalyst;[13] using this modification, reductive coupling of **1a** with α-methyl (**2c**) and α-phenyl (**2d**) benzyl acrylate provided targets **3k** and **3l** in high yield and as single diastereomers (>20:1 d.r.). The relative stereochemistries of **3k** and **3l** were assigned by X-ray diffraction;[14] interestingly, these products possess opposite relative configurations. β-Substituted acrylates also participate, such that targets **3m** and **3n** were formed in 77% and 73% yield, respectively. In the latter case, the Lewis acid co-catalyst was not required, likely due to the high electrophilicity of the acrylate partner, *trans*-dibenzylfumarate **2f** (vide infra).



[a] $Mg(OTf)_2$ (10 mol%) was used as an additive. [b] 600 mol% of acrylate was used.

Table 2. Reductive coupling of benzyl acrylate with isatins.

Our observations are that isatins are privileged substrates for this reductant relay process. Nevertheless, we have established that, in certain cases, other classes of 1,2-dicarbonyl also participate, suggesting potentially wider applications of the strategy. For example, benzil systems **4a-c** generated the corresponding mono-cyclic lactones **5a-c** in modest to very good

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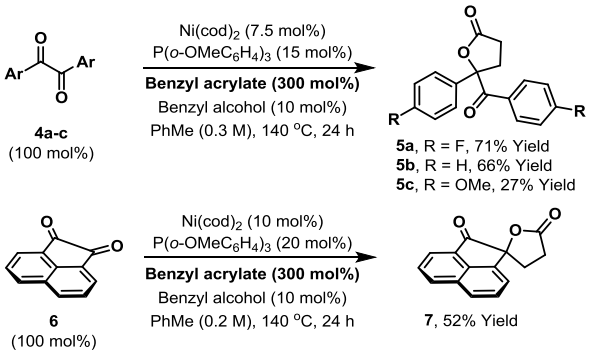
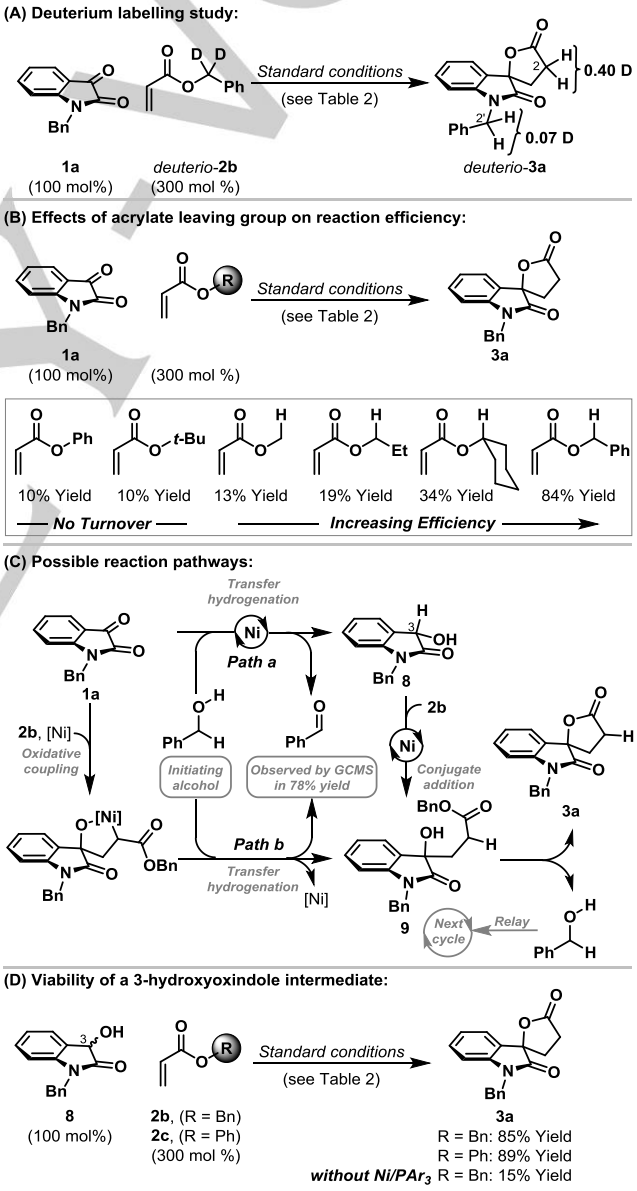
yield (Scheme 3). Cyclic system **6** was also a competent reaction partner, generating lactone **7** in 52% yield when $Mg(OTf)_2$ was used as co-catalyst. As far as we are aware, the examples in Table 2 and Scheme 2 are the first catalytic reductive lactonizations that harness carbonyls and unfunctionalized acrylate esters. Existing non-catalytic protocols use exogenous stoichiometric reductants,[5] whereas catalytic approaches require alcohols as the starting material, which, in turn, mandates prior reduction of the carbonyl partner.[4]



Scheme 2. Reductive coupling of benzyl acrylate with activated ketones.

To probe the mechanism of the process a series of experiments was undertaken. When *deuterio*-**2b**, which incorporates deuterium at the benzylic positions, was exposed to optimized conditions, 40% deuterium transfer to C2 of *deuterio*-**3a** was observed (Scheme 3A). Significant deuterium incorporation was also found at C2', indicating that the Ni(0)-system can also activate the N-benzylic position.[15] For **1a** to **3a** (84 % Yield), GCMS analysis of the crude reaction mixture revealed the concomitant formation of benzaldehyde in 78% yield. These observations show that the benzyloxy unit of the acrylate partner (**2b**) acts as the reductant for C-C bond formation. Under optimized conditions we have confirmed that benzyl acrylates are most effective (Scheme 3B). Other systems with primary or secondary alcohol based leaving groups, such as methyl, ethyl and cyclohexyl acrylate also enabled turnover, but provided **3a** in significantly diminished yields. Conversely, phenyl and *tert*-butyl acrylate, which release "non-oxidizable" phenol or *t*-BuOH, did not allow turnover, with the yield of **3a** limited to the loading of the benzyl alcohol initiator (10 mol%). Overall, these observations are consistent with the reductive formation of γ-hydroxy ester **9**, in advance of lactonization to product **3a** (Scheme 3C). Intermediate **9** might arise via either a carbonyl reduction-conjugate addition pathway (path a)[16] or an oxidative coupling-reduction sequence (path b).[17,18] Two key observations provide circumstantial support for path a: (1) an adjacent acidifying group is required on the carbonyl partner[19] and (2) products of oxidative coupling with the benzaldehyde byproduct are not formed.[20] The beneficial effects of $Mg(OTf)_2$ in certain cases would be consistent with Lewis acid activation of the acrylate for conjugate addition. Exposure of **8** (the reduced form of **1a**) to optimized conditions, with either benzyl (**2b**) or phenyl acrylate (**2c**), generated **3a** in high yield (Scheme 3D). Lactone formation from **8** in the absence of Ni-catalyst was feasible, but resulted in low conversion to **3a** (15% yield). Thus, if path a is operative, the Ni-catalyst must play an intimate role in enhancing the C-C bond forming event. One possibility is that oxidative addition of Ni(0) into the C3-H bond of **8** generates a Ni-enolate; this kind of process has been suggested in other contexts.[21] Exposure of **8** to benzaldehyde (100 mol%) under standard catalytic conditions (in the absence of acrylate) resulted in a 35% yield of **1a**, showing that reduction of **1a** is reversible. Because of this, initial oxidation of **8** to **1a** in advance of spirolactonization via path b cannot be ruled out. As already discussed, Ni(II)-systems or commonly employed Ru- and Ir-based transfer hydrogenation catalysts do not promote the reaction, supporting a role for the Ni(0)-system beyond simply effecting transfer hydrogenation of **1a**.



Scheme 3. Preliminary mechanistic studies.

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According to the mechanistic blueprint outlined in Scheme 1, Eqn. 4, other classes of process might be achievable using a reductant relay approach. Although further expansion of the strategy will require the identification of new catalysts and/or fragment coupling steps, we were keen to uncover additional processes that might be achieved using the Ni(0)-system presented here. Specifically, we envisaged that α-oxo imines might couple with acrylates to provide lactams. This proposition was appealing because only sparse reports document the use of stoichiometric metallic reductants to achieve this seemingly simple process, and no catalytic approaches are available.[7] Pleasingly, when *N*-*p*-methoxyphenyl imine **10a** was exposed to conditions optimized for lactonization, spirocyclic lactam **11a** was generated in 68% yield (Table 3). Further evaluation revealed that this lactamization process has similar scope to the lactonization methodology. Indeed, electronically diverse isatin-based imines **10b-e** all engaged in smooth reductive coupling to provide lactam targets **11b-e** in good to excellent yield. Extension of the protocol to the imine derived from benzil **4b** provided monocyclic system **12** in 68% yield; the alternate lactone product was not observed. We have also investigated a one-pot imine formation-lactamization sequence (Scheme 4). Exposure of isatin **1a** to *p*-methoxyaniline under acidic conditions generated imine **10a**. Removal of the volatile components was followed by direct addition of the reagents required for reductive lactamization, allowing a telescoped synthesis of **11a** in 50% yield over the one-pot, three component process.

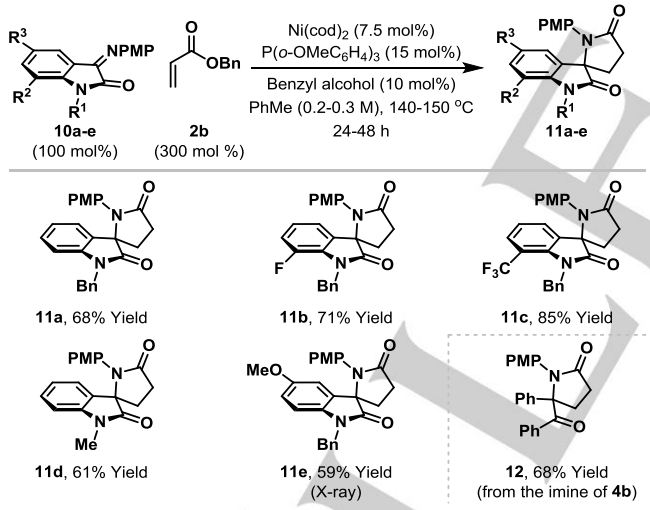
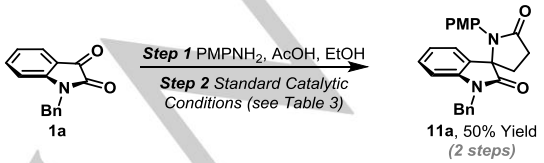


Table 3. Reductive coupling of benzyl acrylate with ketimines.



Scheme 4. One-pot imine formation-lactamization.

In summary, we demonstrate a unique approach to transfer hydrogenative C-C bond formation, wherein the native reducing power of an alcohol released upon lactonization or lactamization is used to drive catalytic turnover. This provides an interesting example of atom economical methodology, highlighting how an otherwise wasted byproduct can be used productively. The studies described here encompass the first catalytic methods for accessing lactones or lactams by the direct reductive coupling of carbonyls/imines with unfunctionalized acrylates. Future studies will seek to identify other catalyst systems that can promote the stereocontrolled coupling of a wider range of reaction partners.

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Keywords: transfer hydrogenation, C-C bond, lactone, lactam

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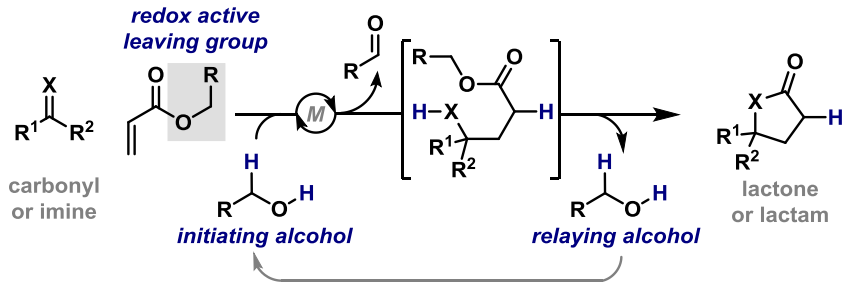

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Ni-catalyzed coupling of benzyl acrylates with activated ketones or imines provides a direct entry to γ-butyrolactones and lactams. The benzyl alcohol byproduct released during the lactonization/lactamization event is relayed to the next cycle where it then serves as the reductant for C-C bond formation.