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Efficient Synthesis of Functionalized 1-oxo-1-phenyl-2-acetic Acids through Ru(II)-catalyzed Transfer Hydrogenation

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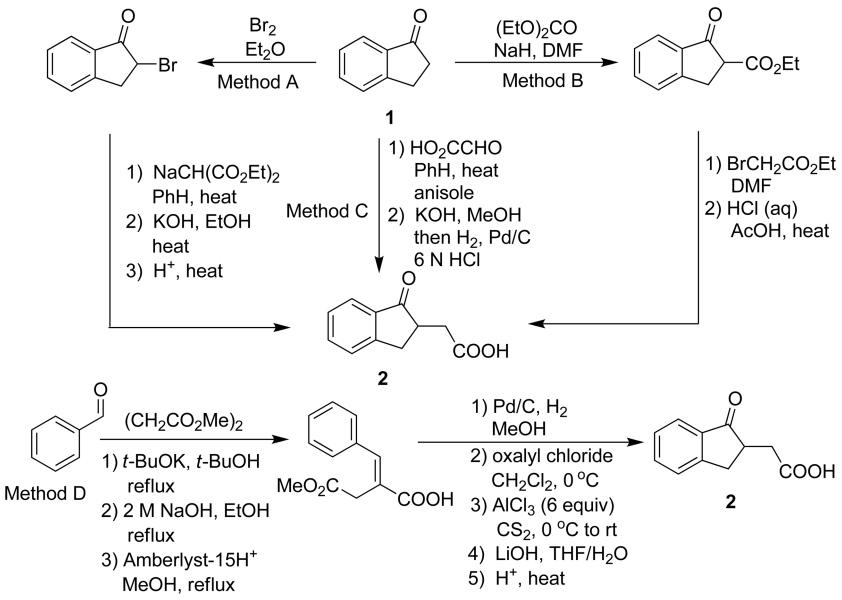
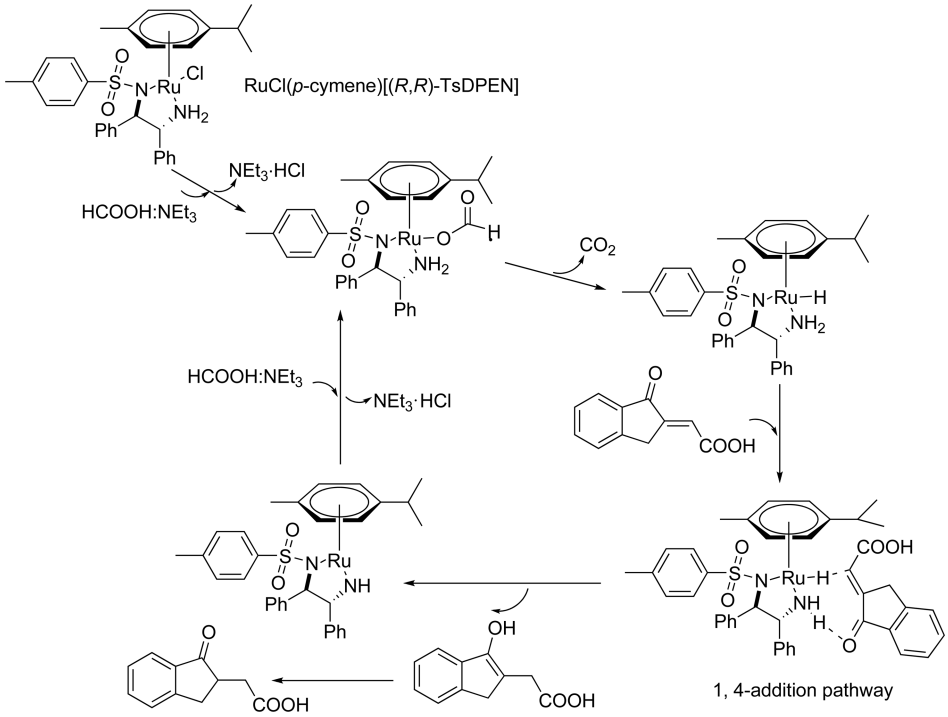
Strigolactone (SL) plays an important role as chemical transmitters not only in rhizosphere but also in the aerial part in plants, and it controls seed germination, stem branching and crop yield.[1-3] The synthetic SL analog, GR24 is a very potent germination stimulant, which is widely used in parasitic weed research to stimulate germination and as a standard for comparison of new germinating agents.[4-6] Owing to the prevalence of GR24, its total synthesis constitutes a hot area of research. So far all known synthetic routes of GR24 used indanylacetic acid **2** as a key intermediate, for which very few methods of building compound **2** have been reported (Scheme 1).[7-10]

Although these examples represent important advances, there remain significant limitations that warrant further method development. For example, in routes A, B and D, environmentally non-compatible solvents were used, stoichiometric amounts of salt wastes were produced, and the longer synthetic steps were involved that lead to the lower yield of **2**. For route C, it gave **2** *via* a two-step process that is the easiest one, but this reaction protocol required special equipment, additional pre-treatment for increasing reaction efficiency of substrate and subsequent involved the handling of potentially hazardous gaseous hydrogen. Thus, a new and alternative method should be need for the efficient synthesis of indanylacetic acid **2**.

The notable feature of chiral TsDPEN-Ru(II) catalysts developed by Noyori is that the transfer hydrogenation reaction is highly chemoselective for the C=O function and tolerant of alkenes. On the contrary, recently Deng and co-workers reported the transfer hydrogenation of activated



Scheme 1. Reported routes for synthesizing indanylacetic acid **2**.



Scheme 2. Proposed mechanism.

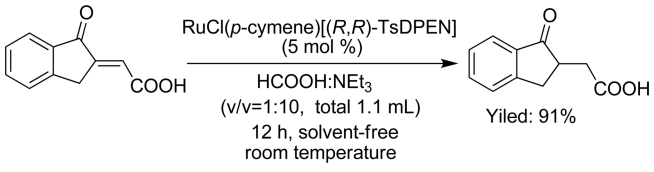
C=C bonds by employing the catalysts,[11] and continuous studies by Deng and others showed that the chemoselectivity could be switched from C=O to C=C bonds through further polarization of the olefins.[12-14] With this background, we hypothesized that the Ru(II) catalyst could perform a specifically selective reduction of C=C bonds in strongly polar (*E*)-2-(1-oxo-1*H*-inden-2(3*H*)-ylidene)acetic acid *via* the transfer hydrogenation pathway, thereby providing the desired indanylacetic acid **2**. To the best of our knowledge, this is the first report on the transfer hydrogenation of such compound using chiral TsDPEN-Ru(II) catalyst.

To test this hypothesis, therefore, a reaction that used (*E*)-(1-oxo-1*H*-inden-2(3*H*)-ylidene)acetic acid as substrate, well known RuCl(*p*-cymene)[(*R*,*R*)-TsDPEN] as the catalyst, and formic acid-triethylamine as the hydrogen source was examined. To our delight, treatment of (*E*)-(1-oxo-1*H*-inden-2(3*H*)-ylidene)acetic acid (0.2 mmol) with formic acid-triethylamine (total 1 mL, v/v = 1:1) in the presence of RuCl (*p*-cymene)[(*R*,*R*)-TsDPEN] (5 mol %) in methanol (0.5 mL) at room temperature for 24 h gave the desired indanylacetic acid **2** in 81% yield and its structure was confirmed by ^{1}H and ^{13}C NMR analysis and mass spectrometry (see Supporting Information). Moreover, the enantioselectivity of this product was tested and the result indicated that it was racemic mixture, which suggested the reduction of C=C bonds *via* the 1,4-addition pathway by using an enol structure as the transition state (Scheme 2).[13-15]

Inspired by the results, we postulated that using [$RuCl_2$(*p*-cymene)]$_2$ instead of chiral TsDPEN-Ru(II) in the same reaction system might lead to the desire product. Hence, we carried out this reaction, and the result showed that, however, in the absence of TsDPEN ligand, the catalytic activity declined sharply with the corresponding decrease of the reduction product. It suggested that the existence of TsDPEN ligand was essential for processing the reaction. In addition, the reaction was performed by using another well known RuCl(*p*-cymene)[(*S*,*S*)-TsDPEN] as the catalyst and it provided indanylacetic acid **2** with the 79% yield. The result showed that the chiral nature of the catalyst might not play a key role in this catalytic system.

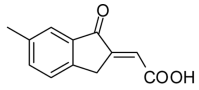
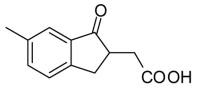
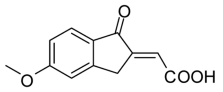
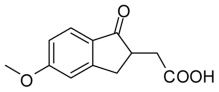
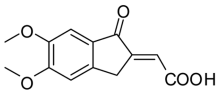
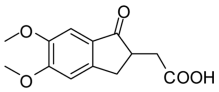
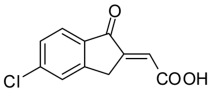
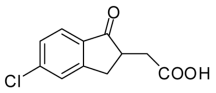
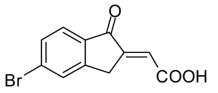
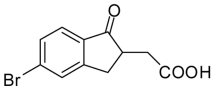
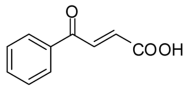
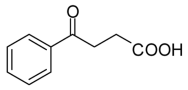
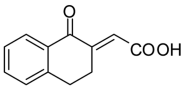
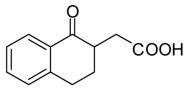
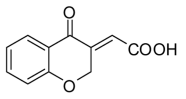
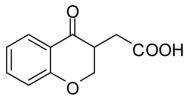
It is well known that the ratio of formic acid-triethylamine is an important parameter for obtaining reasonable quantities of product through transfer hydrogenation. In order to find the optimal ratio, we also carried out a series of parallel reactions by varying the ratio of formic acid-triethylamine from 0 to 2.5. It was found that the rate of the reaction was fastest (time: 12 h, yield: 89%) in 1:10 (v/v, total 1.1 mL) mixture of formic acid and triethylamine.

On the other hand, solvent-free chemistry has attracted much attention recently due to their economic viability and environmental benignness. We were interested in determining the catalytic activity of RuCl(*p*-cymene)[(*R*,*R*)-TsDPEN] catalyst under solvent-free conditions. Very gratifyingly, (*E*)-2-(1-oxo-1*H*-inden-2(3*H*)-ylidene)acetic acid in the presence of no solvent under the optimal condition gave the desired product **2** with excellent yield of 91% (Scheme 3).



Scheme 3. The optimized reaction system.

Table 1. Ru(II)-catalyzed transfer hydrogenation of functionalized (*E*)-2-(1-oxo-1*H*-inden-2(3*H*)-ylidene)acetic acids[a]

Entry	Substrate	Product	Yield[b]
1			85%
2			75%
3			61%
4			72%
5			78%
6			82%
7			95%
8			35%

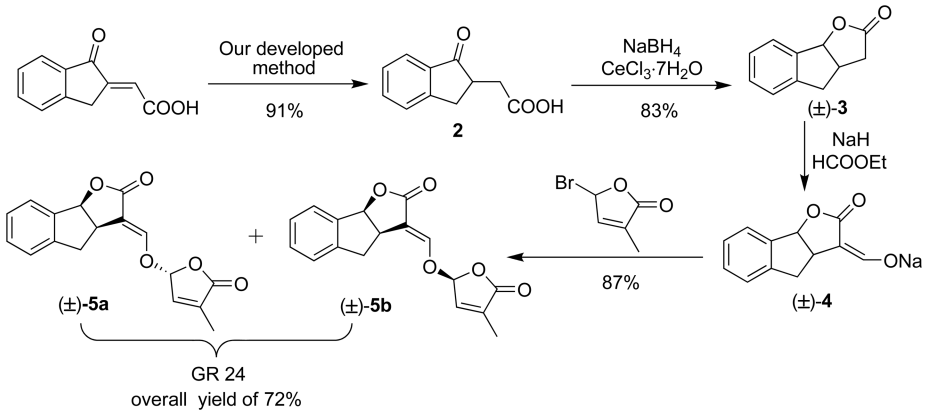
[a]Reaction conditions: substrates (0.2 mmol), Ru catalyst (5 mol %), and formic acid-triethylamine (total 1.1 mL, v/v = 1:10), no solvent, room temperature, 12 h. [b]Isolated yields.

With the optimized catalytic system in hand, and in order to demonstrate the usefulness of the developed method, firstly we probed its versatility in the selective reduction of the C=C bonds in varieties of functionalized (*E*)-2-(1-oxo-1*H*-inden-2(3*H*)-ylidene)acetic acid derivatives. The results were demonstrated in Table 1. Notably, the catalytic system was widely applicable to these substrates, enabling the efficient conversion of both electron-rich acids (entries **1**-**3**) as well as electron-deficient derivatives (entries **4** and **5**). Tolerance to the chloro and bromo functions was especially noteworthy since they are useful for subsequent cross-coupling reactions.

Next, we examined the Ru(II)-catalyzed transfer hydrogenation of several selected 1-oxo-1-phenyl-2-ethylene acids, which represent an important motif in medicinal chemistry. Typical results were summarized in Table 1 (entries **6**-**8**). We were pleased to find that the catalytic system worked well on 4-oxo-4-phenyl-2-butenoic acid (entry **6**), and 2-(1-oxo-3,4-dihydro-2(1*H*)-naphthalenylidene)acetic acid (entry 7). The method was also successfully extended to (3-oxo-2(3*H*)-benzofuranylidene)-acetic acid (entry **8**). In the present cases, all C=C bonds were reduced selectively by using our developed procedure and the corresponding saturated ketone acids were isolated as the desired products with up to yield of 95%.

Finally, we sought to demonstrate the application of our methodology in the total synthesis of the important strigolactone analogue GR24. As shown in Scheme 4, using our obtained indanylacetic acid **2** as starting material led to the total synthesis of GR24 [diastereoisomers (±)-**5a** and (±)-**5b**] in three steps with an overall isolated yield of 72% on the gram scale. Analytical data were in agreement with those reported in the literature (see Supporting Information).[7-10] Co-crystal structures of our synthesized GR24 and OsD14 revealed unique pocket topologies as a basis for SL signaling specificities and identified the pathway and mechanism of D14-catalyzed GR24 hydrolysis.[16]

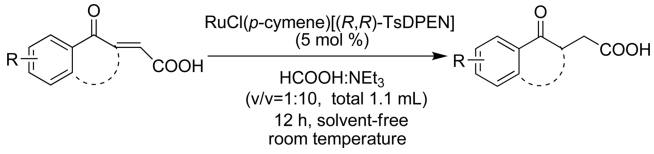
In summary, a new and alternative method for the efficient synthesis of indanylacetic acid **2** has been developed. The methodology used RuCl(*p*-cymene)[(*R*,*R*)-TsDPEN] as the catalyst and formic acid-triethylamine as the hydrogen source at room temperature under solvent-free conditions, and the reactions have excellent chemoselectivity and good compatibility of substrates. Used our developed method as the starting step, gram scale synthesis of GR24 was achieved smoothly with an overall yield of 72%. All the results suggested that further development of such methodology may be of interest. Further work to establish the mechanistic reasons for selectivity and to further explore the synthetic scope of this mode of transfer hydrogenation is in progress.



Scheme 4. The total synthesis of GR24 using our developed methodology as the starting step.

Experimental

General Procedure for Preparation of Functionalized 1-Oxo-1-phenyl-2-acetic Acids.



To a 10 mL sealed-tube were added substrate (0.2 mmol), Ru catalyst (5 mol %), and formic acid-triethylamine (total 1.1 mL, v/v = 1:10), at room temperature. The tube was sealed and stirred at room temperature for 12 h. The resulting mixture was acidified with 1 M HCl to PH < 7. Then the mixture was extracted with ethyl acetate, the organic layer was dried over anhydrous Na_2SO_4 and concentrated on rotary evaporator under reduced pressure. Finally, the residue was purified by silica gel column chromatography to give the desired product.

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Supporting Information. General methods, materials, and Characterization data of related compounds were attached.

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