Reductive Passerini/Tsuji–Trost Strategy towards β,γ-Unsaturated Amides

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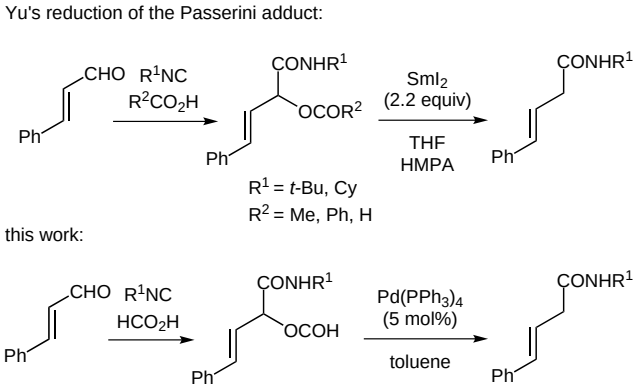
Abstract: The Passerini reaction of α,β-unsaturated aldehydes with formic acid followed by a reductive Tsuji–Trost reaction affords β,γ-unsaturated amides. The overall process may be viewed as a one-carbon homologation of unsaturated aldehydes into amides.

Key words: palladium, multicomponent reaction, reduction, allyl complexes, tandem reaction

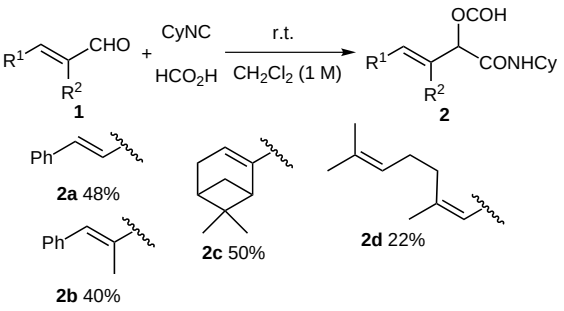
The Passerini and the Ugi reactions constitute the backbone of isocyanide-based multicomponent reactions (IMCR).[1] Compared to the four-component Ugi reaction discovered nearly forty years later, the three-component Passerini reaction has been the object of much fewer applications.[2] This may be explained by the reduced number of components making the process less effective for library preparation but also by a more demanding activation of the aldehyde towards the moderately nucleophilic isocyanide. Among the strategies taking advantage of the acyloxy function of Passerini adducts, the Passerini–amine deprotection–acyl migration (PADAM) protocol[3] is of particular interest together with the reduction of specific Passerini adducts either with zinc in ethanol[4] or with samarium iodide.[5] In the latter case the reaction was performed on Passerini adducts of cinnamadehyde forming β,γ-unsaturated amides through cleavage of the ester moiety derived from starting acetic, benzoic, or formic acids. Considering the Passerini adduct of cinnamaldehyde and formic acid, we envisaged that the reductive process could be significantly improved using the formic ester as an situ reductant in a Tsuji-type reductive reaction (Scheme 1).[6] To the best of our knowledge, Tsuji–Trost-type allylation has never been disclosed on Passerini adducts as substrates. Thus, assessment of the efficiency and regiochemistry of the reductive allylation would be of interest and might give some good indications for further use of Passerini adducts with other nucleophilic species.

The preparation of a variety of allylic formates was therefore undertaken to test the subsequent Tsuji–Trost procedure. Initial trials for the Passerini reaction working under molar conditions in CH_2Cl_2 were rather disappointing, forming allylic formates **2a–d** from aldehydes **1a–d** in only moderate yields after 24 hours at 25 °C (Scheme 2). The solvent-free conditions recently reported for the Passerini reaction[7] did not improve the reaction. Indeed, on



Scheme 1 Reduction of cinnamaldehdye Passerini adducts

adding formic acid to a neat mixture of cinnamaldehyde (**1a**) and cyclohexyl isocyanide, the latter was completely consumed leaving a large amount of starting aldehyde and forming **2a** in just a 50% isolated yield.



Scheme 2 Passerini adduct **2a–d** from formic acid

The Passerini reaction involving formic acid is known to be highly efficient for rather electrophilic carbonyl derivatives.[8] However, for less reactive aldehydes, yields are usually much lower than with acetic acid.[9] This is probably due to the higher instability of the isocyanides in the presence of the more acidic formic acid. This behavior had been confirmed by Nef as early as 1892 when he noted that formic acid reacted explosively with phenyl isocyanide under neat conditions at 0 °C with formation of aniline formamide; whereas acetic acid reacted smoothyl at room temperature with the same isocyanide.[10]

Considering the moderate stability of isocyanides towards formic acid, we decided to perform the reaction with α,β-unsaturated aldehydes in CH_2Cl_2 (1 M) with an excess of both isocyanide and formic acid (1.6 equiv). Best yields were obtained when the mixture was left two days at room temperature (Table 1).

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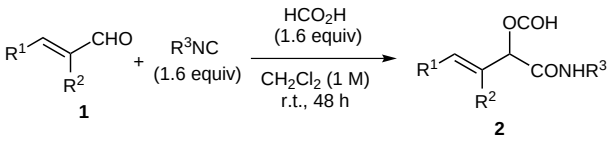
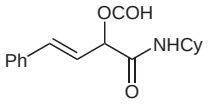
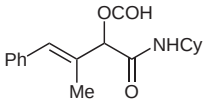
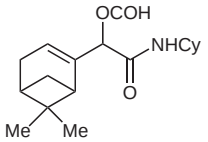
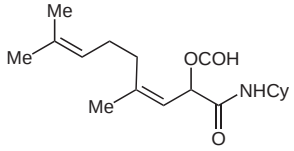
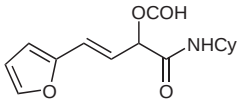
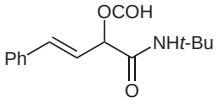
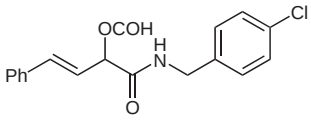
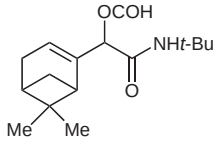
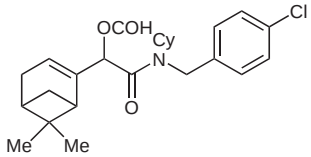
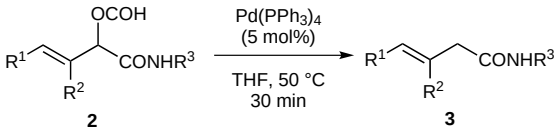
Table 1 Synthesis of Passerini Adducts **2**



Entry	**2**	Yield of **2** (%)
1	 **2a**	83
2	 **2b**	55
3	 **2c**	66
4	 **2d**	65
5	 **2e**	46
6	 **2f**	54
7	 **2g**	49
8	 **2h**	64
9	 **2i**	57

Cyclohexyl isocyanide and cinnamaldehyde gave a good yield of over 80% (Table 1, entry 1). For other α,β-unsaturated aldehydes and isocyanides, some aldehyde still remained unreacted in the mixture even after two days of reaction (Table 1, entries 2–9). The resulting allylic formates **2a**–**i** were next treated with a catalytical amount of $Pd(PPh_3)_4$ in warm THF, a classical condition for Tsuji–Trost-type allylation.[6] Except for amide **2d**, which gave a complex mixture of isomers, all amides were cleanly converted within less than 30 minutes at 50 °C to the reduced amides **3a**–**i** (Table 2) formed as a single regioisomer.

Table 2 Synthesis of Amides **3**

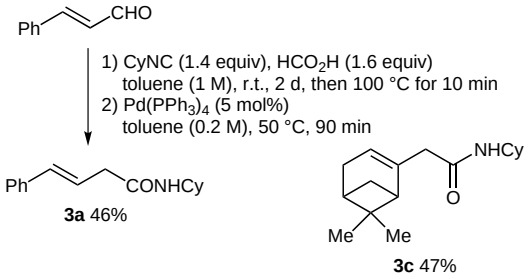


Entry	Starting formate **2**	Yield of product **3** (%)
1	**2a**	**3a** 86
2	**2b**	**3b** 89
3	**2c**	**3c** 77
4	**2d**	–
5	**2e**	**3e** 69
6	**2f**	**3f** 84
7	**2g**	**3g** 75
8	**2h**	**3h** 80
9	**2i**	**3i** 76

The Tsuji–Trost reduction with formic acid or formate esters is usually highly regioselective, the hydride attacking the more hindered position of the η^3-allyl system. In the case of aryl-substituted alkenes (Table 2, entries 1, 2, 5–7), the formation of the conjugated alkene may be explained by a reduction involving a more stable η^1-allyl palladium formate complex as previously observed by Backvall et al.[11] The regioselectivity observed for **2c** might be explained using similar arguments with the double bond preferring an endocyclic position. Chelation with the amide function might be involved as well but trials with other α,β-unsaturated aldehydes should be made to confirm this behavior.

To improve the efficiency of the process, we then tried to perform the two steps in the same pot. When cinnamaldehyde was left for two days with 1.6 equivalents of both cyclohexyl isocyanide and formic acid in dichloromethane, addition of toluene and catalyst (5 mol%) did not result in any transformation of intermediate **2a**. A further 5 mol% of palladium catalyst needed to be added to the mixture to observe the formation of **3a** obtained in 44% isolated overall yield. Taking into account the deleterious effect of residual isocyanide on the activity of $Pd(PPh_3)_4$, we decided to modify the procedure. The first step was performed

in toluene (toluene and CH_2Cl_2 give similar yields of **2a** from cinnamaldehyde) adding a slight excess of formic acid. After two days, toluene was further added and the mixture heated to 100 °C for ten minutes before adding the catalyst. These conditions ensure the destruction of any remaining isocyanide and after cooling, we could observe the conversion of **2a** into **3a** with the same amount of catalyst as when performed previously (Scheme 3). Myrtenal behaved similarly forming **3c** in 47% isolated yield.



Scheme 3 One-pot Passerini/Tsuji–Trost reduction

In conclusion, we have developed for the first time a Passerini/Tjusi–Trost tandem protocol. The choice of formic acid allows the direct reduction of the Passerini adduct without further addition of reductant. Though the synthetic potential of the process is lowered by the moderate yields observed in the Passerini step with formic acid, further extension using acetic acid together with formic acid as an external reducing agent may be envisaged. More interestingly, this preliminary study opens the way to related strategies using carbon-based nucleophiles in the Tsuji step. These last possibilities should increase significantly the diversity offered by the Passerini reaction. We will report further results following this direction in due course.

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Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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Graphical Abstract