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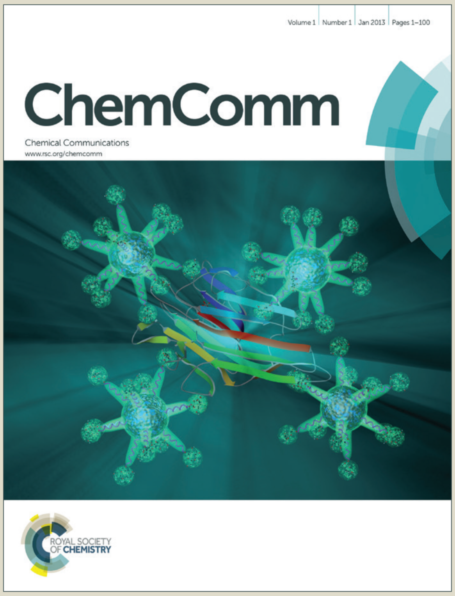

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When Tsuji-Trost meets Passerini!

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Passerini/Tsuji-Trost strategies towards lactams and cyclopentane derivatives.

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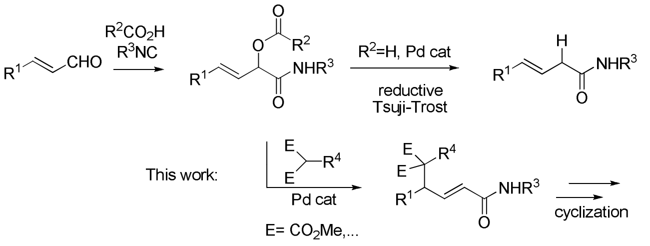
((Dedication----optional))

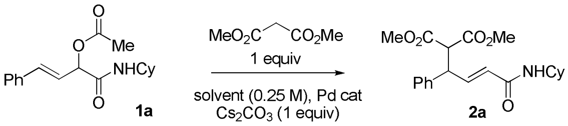
The Passerini and the Ugi reactions certainly represent the most important applications of isocyanides in synthesis.[1] Compared to the Ugi reaction, the use of the Passerini coupling[2] has been limited by its 3-component nature together with a poorer efficiency. Indeed, the instability of isocyanides under highly acidic conditions and the need for an efficient electrophilic activation of the carbonyl moiety often limits the synthetic scope of the Passerini coupling. In comparison, the addition of isocyanides to the more basic imines is easily achieved under moderately acidic conditions in the Ugi process. As a consequence most uses of isocyanides in MCRs mainly involve an Ugi reaction as the key step. However, several strategies involving transformation of the ester moiety of Passerini adducts have allowed to highlight the benefits of this coupling. This is the case of the Passerini-amine deprotection-acyl migration (PADAM) protocol[3] or the reduction of various Passerini adducts with zinc in ethanol [4] as well as samarium iodide.[5] With this idea in mind, we have recently disclosed a reductive Tsuji-Trost transformation of cinnamaldehyde derived Passerini adducts (Scheme 1).[6]



Scheme 1. Tsuji-Trost reaction of Passerini adducts

Though the latter reductive transformation displays the first use of a Passerini adduct in a Tsuji-Trost reaction,[7] the synthetic scope of the process was quite limited and we were eager to develop a version of this reaction with carbon based nucleophiles in order to raise the diversity offered by the tandem (Scheme 1). Herein, we wish to present our first results obtained with malonate derivatives as well as their extension to Tsuji-Trost/Michael addition tandems.

Malonic esters certainly represent the most thoroughly developed nucleophiles in Tsuji-Trost reactions, simple methyl malonate was thus first chosen to test the behavior of Passerini adduct **1a** formed from cinnamaldehyde, acetic acid and cyclohexyl isocyanide. Under treatment with a Pd(OAc)$_2$/PPh$_3$ couple under microwave conditions, the malonyl derivative **2a** was obtained in a moderate 54% isolated yield. The following trials under various thermal and microwave conditions allowed us to raise this yield up to 77% working with Pd(Ph$_3$)$_4$ in toluene at 50°C (Scheme 2).



Pd(OAc)$_2$, 5 mol%, PPh$_3$ 10 mol% Toluene (130°C, υW, 15 min):	54%
Pd(OAc)$_2$, 5 mol%, dppe 5 mol% Toluene (130°C, υW, 15 min):	65%
Pd(dba)$_2$, 5 mol%, dppe 5 mol% Toluene (130°C, υW, 15 min):	45%
Pd(PPh$_3$)$_4$, 5 mol%, Tol (50°C, 30 min):	77%
Pd(PPh$_3$)$_4$, 5 mol%, CH$_3$CN (50°C, 30 min):	45%
Pd(PPh$_3$)$_4$, 5 mol%, DMF (50°C, 30 min):	45%

Scheme 2. Optimisation towards Tsuji-Trost adduct **2a**

The latter conditions were selected to evaluate the reactivity of Passerini adducts of various α,β-unsaturated aldehydes in Tsuji-Trost reactions with malonic esters (Table 1). The Passerini esters **1a-m** were all obtained in moderate to good yields reacting the three components for one day at room temperature under solvent free conditions. All the Passerini adducts formed reacted under Tsuji-Trost conditions with dimethyl malonate to give the corresponding α,β-unsaturated amides **2a-m** in good to moderate yields. Thought the regioselectivity of the malonyl attack is opposite to the one obtained in the Tsuji-Trost reduction of Passerini formic esters,[6] it corresponds to the usual behaviour of susbtituted allylic esters towards malonic derivatives. The choice of benzoic acid as carboxylic component of the Passerini step leads to a less efficient Tsuji-Trost reaction (Table 1, entry 2). All other Passerini adducts were thus prepared with acetic acid. Starting from cinnamaldehyde, good yields were obtained for both steps of the tandem with a variety of isocyanides (cyclohexyl, *t*-butyl, benzylic ...Table 1 entries 1-6). Cinnamaldehydes susbtituted by an electrondonating group at the 4 position (Table 1, entry 7) or an electronwithrawing group at the 2 position (Table 1, entries 8,9) of the aryl ring gave Passerini adducts in moderate yields but the latter behaved well in the following Tsuji step. The tandem is not limited to cinnamaldehyde derivatives as shown by the formation of the

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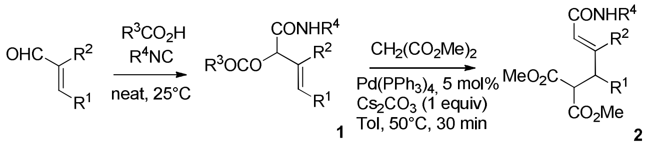
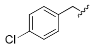
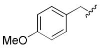
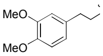
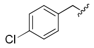
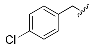
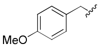
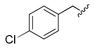
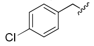
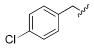
[**] Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

malonyl derivative **2m** obtained in moderate yield from Passerini adduct **1m** as well as furyl derivatives **2j** and **2k**.

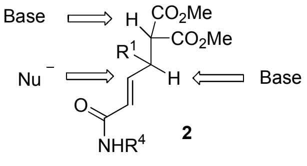
Table 1.Scope of Passerini/Tsuji-Trost tandem with dimethylmalonate



Entry	R^1	R^2	R^3	R^4	**1** (Yield %)	**2**[a] (Yield %)
1	Ph	H	Me	Cy	**1a** (94)	**2a** (77)
2	Ph	H	Ph	Cy	**1b** (94)	-
3	Ph	H	Me	*t*-Bu	**1c** (73)	**2c** (87)
4	Ph	H	Me		**1d**(90)	**2d** (69)
5	Ph	H	Me		**1e** (87)	**2e** (78)
6	Ph	H	Me		**1f** (76)	**2f** (72)
7	4-(MeO)C_6H_4	H	Me		**1g** (65)	**2g** (75)
8	2-(NO_2)C_6H_4	H	Me		**1h** (65)	**2h** (67)
9	2-(NO_2)C_6H_4	H	Me		**1i** (57)	**2i** (74)
10	2-furyl	H	Me		**1j** (62)	**2j** (37)
11	2-furyl	H	Me	Cy	**1k** (46)	**2k** (74)
12	Ph	Me	Me		**1l** (75)	**2l** (73)
13	n-Pr	H	Me		**1m** (71)	**2m** (43)

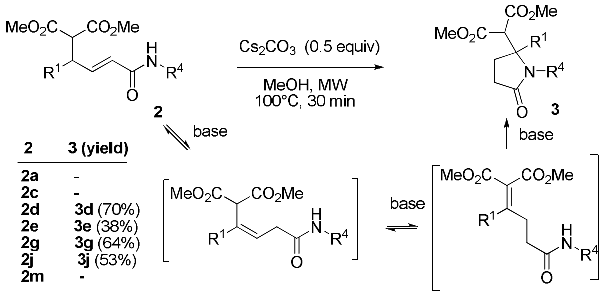
[a]:for R^2=H, all alkenes **2** have a trans configuration ($^3J_{HH}$ around 15Hz). The configuration of **2l** has not been determined.

Beyond the interest of a one step preparation of suitable precursors for Tsuji-Trost couplings, this strategy leads to an efficient synthesis of ambident species prone to act both as nucleophiles (through deprotonation) and electrophiles (via the α,β-unsaturated amide moiety) under suitable activation (Scheme 3). Besides the C-H malonyl bond, we envisioned that depending on the nature of the R^2 group, the allylic C-H bond could be also activated under basic conditions.



Scheme 3. Reactivity pattern of Tsjui-Trost adduct **2**

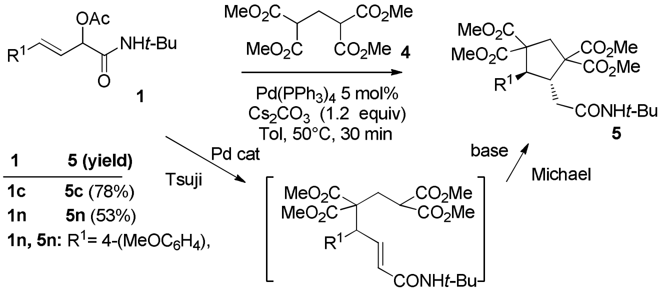
This acidic property of the allylic C-H position was best pictured by the conversion of **2d** into lactam **3d** under microwave heating with Cs_2CO_3 at 100°C in methanol (Scheme 4). Under these protic conditions, a set of equilibria are probably settled leading to the migration of the double bonds towards the malonyl moiety. These equilibria are finally shifted by a Michael addition towards lactams **3**. The reaction is quite sensitive to the nature of the nitrogen substituent, with a *t*-butyl or cyclohexyl group tethered on the nitrogen amide, no reaction occurred. The same is observed when the aryl R^2 group is replaced by an aliphatic group making the position less acidic.



2	3 (yield)
2a	-
2c	-
2d	**3d** (70%)
2e	**3e** (38%)
2g	**3g** (64%)
2j	**3j** (53%)
2m	-

Scheme 4. Lactams **3** from Tsuji-Trost adducts **2**

In order to gain more opportunities to express the electrophilic properties of the α,β-unsaturated amide moiety of **2**, we decided to extent the study to the use of bis-nucleophiles in the Tsuji-Trost step. According to the length of the tether between the two nucleophilic sites, this approach could offer a fast assembly of cyclopentanes, cyclohexanes or even larger rings. To prove the concept, the bis-malonyl ester **4** was prepared from dimethyl malonate and diiodomethane.[8] When **4** was added to N-*t*-Butyl Passerini adducts **1c** and **1n** under the Tsuji-Trost conditions settled previously, we were delighted to observe the direct formation of substituted cyclopentanes **5c** and **5n** through a Tsuji-Trost/Michael addition cascade (Scheme 5). The assumed trans configuration of **5c** and **5n** was consistent with a 13 Hz coupling constant of the two trans cyclopentyl hydrogen together with a Noesy correlation between the latter and hydrogens of the aryl moiety. Due to the know flexibility of cyclopentyl rings, these elements however were not sufficient to ascertain the trans relation between the aryl and amide moieties.



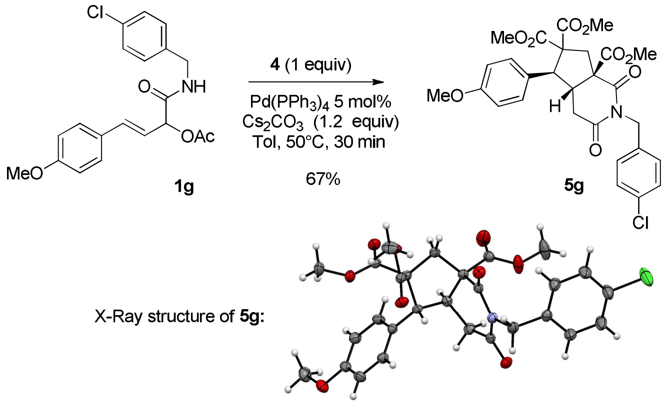
1	5 (yield)
1c	**5c** (78%)
1n	**5n** (53%)

1n, 5n: R^1= 4-($MeOC_6H_4$),

Scheme 5. Tsuji-Trost/Michael cascade towards cyclopentanes **5**

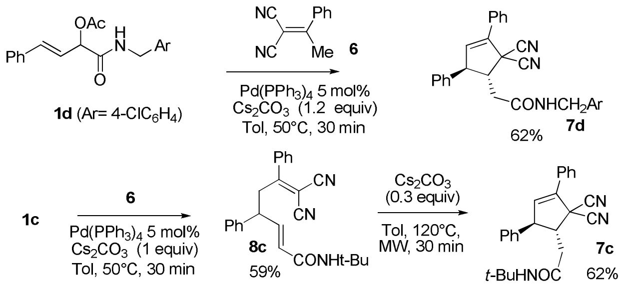
A further confirmation was obtained working with the less sterically hindered Passerini amide **1g**. In the latter case, a more complex cascade involving all functionalities of the Passerini adduct is observed during the Tsuji-Trost step (Scheme 6). The fused cyclopentanopiperidinedione **5g** was obtained via a final condensation of the intermediate cyclopentyl N-benzyl amide with a vicinal ester moiety. In contrast with the previous oily cyclopentane derivatives, the cyclic diimide **5g** gave crystals in methanol solutions and its structure could be confirmed by Xray crystallography (Scheme 6).[9]

If these new cascades significantly extent the synthetic potential of the Passerini reaction, the interest of the study is not limited to the field of isocyanide based multicomponent reactions. Indeed, the formation of cyclopentane derivatives using a bis-nucleophile in a Tsuji-Trost reaction has only been documented with propargylic esters with reaction mechanisms specific to the alkyne moiety.[10]



Scheme 6. Tsuji-Trost/Michael cascade towards diimide **5g**

This strategy may be easily extended to other families of bis-nucleophiles such as the malonitrile derivative **6** (Scheme 7). The latter, easily formed under condensation of acetophenone with malonitrile, reacts with Passerini adduct **1d** to form the cyanosubstituted cyclopentene **7d** in a 62% isolated yield.



Scheme 7. Tsuji-Trost/Michael cascade towards cyclopentanes **7**

The direct formation of the cyclopentane ring under the Tsuji-Trost condition is not as general as observed for the bis-malonyl derivative **4**. If **7d** is directly obtained from **1d**, when the same conditions are applied to **1c** as starting material, the intermediate **8c** is reluctant to cyclize at 50°C and could be isolated in 59% yield. It could however be transformed to cyclopentane **7c** at higher temperature.

In conclusion, we have disclosed new Tsuji-Trost transformations of Passerini adducts derived from α,β-unsaturated aldehydes. This preliminary report opens the way to the use of many different carbon based nucleophiles leading to a significant extension of the structural diversity offered by the Passerini coupling. The synthetic power of this approach is further highlighted by the use of bis-nucleophiles in the Tsuji-Trost step allowing further reaction of the intermediate α-β unsaturated amides. New Tsuji-Trost/Michael addition cascades lead then to a very straightforward access to cyclopentane derivatives. We will further explore the extension of such approaches to the formation of cyclohexane derivatives through proper choice of the bis-nucleophile as well as extensions to other multicomponent reactions of cinnamaldehydes .

Experimental Section

Typical procedure given for **2a, 5g:** To a 0.25 M solution of Passerini adduct **1a** (1.0 equiv.) in toluene were added dimethyl malonate (1.0 equiv), Cs_2CO_3 (1.0 equiv) and $Pd(PPh_3)_4$ (5 mol %). The resulting mixture was stirred at 50°C during 30 minutes. Removal of the solvent and purification by flash chromatography with Et_2O/Petroleum Ether (20/80 to 80/20 gradient) as eluant gave the desired product (190 mg, 77%) as an yellow solid. **CCM** Rf (80/20 Et_2O/EP) = 0.20 ; **Mp:** 151 – 152°C ; **^{1}H-NMR (δ, ppm)** ($CDCl_3$, 400 MHz) 7.33 (m, 2H), 7.29 (d, J=5.2Hz, 1H), 7.25 (m, 2H), 6.93 (1H, dd, J=14.8, 8.0Hz, 1H), 5.78 (d, J=15.2Hz, 1H), 5.33 (d, J=8.0Hz, 1H), 4.25 (t, J=11.2Hz, 1H), 3.92 (d, J=11.2Hz, 1H), 3.82 (m, 1H), 3.77 (s, 3H), 3.50 (s, 3H), 1.92 (m, 2H), 1.72 (m, 2H), 1.63 (m, 2H), 1.35 (m, 2H), 1.15 (m, 2H) ; **^{13}C-NMR (δ, ppm)** ($CDCl_3$, 100.6 MHz) 168.0 (Cq), 167.5 (Cq), 164.1 (Cq), 142.1 (CH), 138.5 (Cq), 128.9 (2CH), 128.2 (2CH), 127.6 (CH), 125.9 (CH), 56.9 (CH), 52.8 (CH_3), 52.6 (CH_3), 48.3 (CH), 48.0 (CH), 33.1 ($2CH_2$), 25.5 (CH_2), 24.8 ($2CH_2$) ; **IR** (υ, cm^{-1}) 3274, 2930, 2853, 1737, 1667, 1626, 1541, 1452, 1434, 1255, 1152 ; **HRMS** (EI) Calcd. for $C_{21}H_{27}NO_5$: 373.1889 found : 373.1887.

The same procedure using **1g**, Cs_2CO_3 (1.2 equiv) and the bis-malonyl **4** gave the diimide **5g** (159 mg, white crystals, 67%) after purification by flash chromatography with AcOEt/Petroleum Ether (from 10/90 to 50/50) as eluant. **CCM** Rf (50/50 AcOEt/EP) = 0.37 ; **Mp** 134 – 136°C ; **^{1}H-NMR (δ, ppm)** ($CDCl_3$, 400 MHz) 7.27 (s, 4H), 7.10 (d, J=8.8Hz, 2H), 7.07 (d, J=8.8 Hz, 2H), 5.01 (d, J=14.4Hz, AB system, 1H), 4.92 (d, J=14.4Hz, AB system, 1H), 3.82 (d, J=12.8 Hz, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 3.51 (d, J_{AB}=14.8 Hz, 1H), 3.17 (d, J_{AB}=14.8 Hz, 1H), 3.14 (s, 3H), 3.09 (dd, J=12.0, 5.6 Hz, 1H), 2.86 (dd , J=18.4, 6.4 Hz, AB system, 1H), 2.54 (dd , J=18.4, 6.4 Hz, AB system, 1H) ; **^{13}C-NMR (δ, ppm)** ($CDCl_3$, 100.6 MHz) 171.6 (Cq), 170.0 (2Cq), 169.9 (Cq), 169.4 (Cq), 159.3 (Cq), 135.1 (Cq), 133.3 (Cq), 130.0 (2CH), 129.9 (2CH), 128.5 (2CH), 127.4 (Cq), 114.0 (2CH), 63.0 (Cq), 58.5 (Cq), 55.3 (CH_3), 53.6 (CH_3), 53.5 (CH_3), 53.3 (CH), 52.6 (CH_3), 43.2 (CH_2), 42.3 (CH), 40.8 (CH_2), 31.1 (CH_2) ; **IR** (υ, cm^{-1}) 3002, 2953, 2840, 1726, 1677, 1610, 1514, 1433, 1089 ; **HRMS** (EI) Calcd. for $C_{29}H_{32}ClNO_{10}$: 589.1715 found : 589.1721

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[9] The crystallographic data can be obtained free of charge under the reference CCDC 1044250 at the Cambridge Crystallographic Data Centre (www.ccdc.cam.ac.uk/data_request_cif)

[10] For reviews on Pd-catalyzed propargylation, see: (a) J. Tsuji, Palladium Reagents and Catalysts: New Perspectives for the 21st Century; John Wiley & Sons Ltd.: Chichester, West Sussex, England, 2004; pp 543-562. (b) S. Inuki, *Platinum Metals Rev*. **2012**, *56*, 194-199. (c) M. Yoshida, *Chem. Pharm. Bull.* **2012**, *60*, 285-299.

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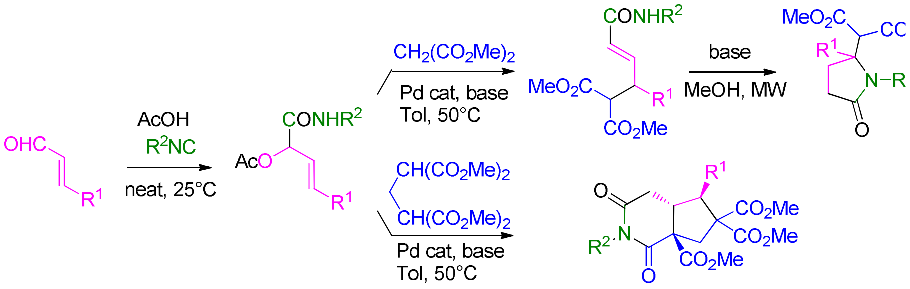
When Tsuji-Trost meets Passerini!

M. Cordier, A. Dos Santos, L. El Kaim,*
N. Narboni__________ **Page – Page**

Passerini/Tsuji-Trost strategies towards lactams and cyclopentane derivatives.



The Passerini reaction of α,β-unsaturated aldehydes affords suitable substrates for Tsuji-Trost reaction with various carbon based-nucleophiles. The resulting α,β - unsaturated amides may be cyclized to lactams or converted into cyclopentane derivatives if bis-nucleophiles are used in the Tsuji-Trost step.