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# Synthesis of non-equivalent diamides and amido-esters via Pd-catalysed carbonylation

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Given the widespread use of amides in chemistry and biology, the development of methods for their synthesis remains important. Although the construction of amide bonds has in principle been known since Wöhler's urea synthesis, the direct and atom-efficient preparation of amides, especially with multiple amido groups, continues to be difficult. To address this challenge, we developed an efficient access to heterobifunctional compounds through linking amines as well as alcohols with specific molecular pincers in the presence of advanced carbonylation catalysts. In detail, we describe the synthesis of non-symmetrical diamides and amido-esters from available propargylic acetates using selective palladium-catalysed diamino- and amino-alkoxy carbonylations. Mechanistic studies and control experiments reveal a cascade process with allenoic amides, allylic amine and dienamide as crucial intermediates. The generality of this protocol is showcased by the highly selective synthesis of >100 heterobifunctional molecules including many pharmaceutically relevant products.

Amide bonds, as the backbone of proteins, not only play a crucial role in elaboration and composition of biological systems but are also present in most pharmacologically active compounds and materials, for example, hydrogels, artificial silks and biocompatible matrices for cell growth[1]. Indeed, amides are identified as the most frequently occurring functional group in ~40% of 420,000 bioactive molecules or two-thirds of drug candidates, and represent 25% of all pharmaceuticals currently on the market according to surveys in 2006 and 2020 (refs. 2–4). In addition, in 2014, >50% of the reported reactions in process chemistry of the pharmaceutical industry used amidation reactions[5]. This demand for amide synthesis encourages constant efforts towards the development of advanced synthetic methods and the construction of new amides. In this respect, diamide and amido-ester derivatives, which are widely distributed in many natural products, are also important in pharmaceutical chemistry[6–11]. For example, several top-selling drugs such as apixaban[6], penicillin[7] and diltiazem[8], as well as the oral anti-COVID-19 drug Paxlovid[9], possess diamide and amido-ester units (Fig. 1a).

Despite the importance of amides in organic chemistry, most of the well-established methods for their formation are relatively inefficient and co-produce large quantities of potentially hazardous waste products. In addition, the purification of the desired amide product can be tedious and difficult[12–15]. This is particularly true for the preparation of non-symmetrical diamide derivatives (Fig. 1b). Traditionally, multi-step synthesis and well-designed or previously functionalized specific starting materials are required for the synthesis of non-symmetrical diamides to avoid the generation of monoamides, symmetrical diamides and other undesirable by-products[16–19]. As an example, for preparation of non-symmetrical terephthaldiamides, it takes six steps to prepare the corresponding product, starting from commercially available *p*-phthaloyl chloride (Fig. 1c)[19]. Indeed, the simple treatment of *p*-phthaloyl chloride[20] with two different amines, for example, *n*-hexylamine and *N*-methylaniline, led to a complex mixture. Likewise, the direct preparation of non-symmetrical diamides of other dicarboxylic acids, for example, malonic acid[21] and phthalic anhydride[22], gave no desired diamides after common amide bond formation reactions (Supplementary Figs. 1–3). Thus, a straightforward and chemoselective synthesis of diamides by joining two different amines with similar reactivities is still in high demand.

In the field of proteomics and medical chemistry, the bio-orthogonal conjugation strategy of *N*-hydroxysuccinimide (NHS) esters with amines (famous as click chemistry and bio-orthogonal chemistry), highlighted by the Nobel Prize in 2022, allows linkage of chemical

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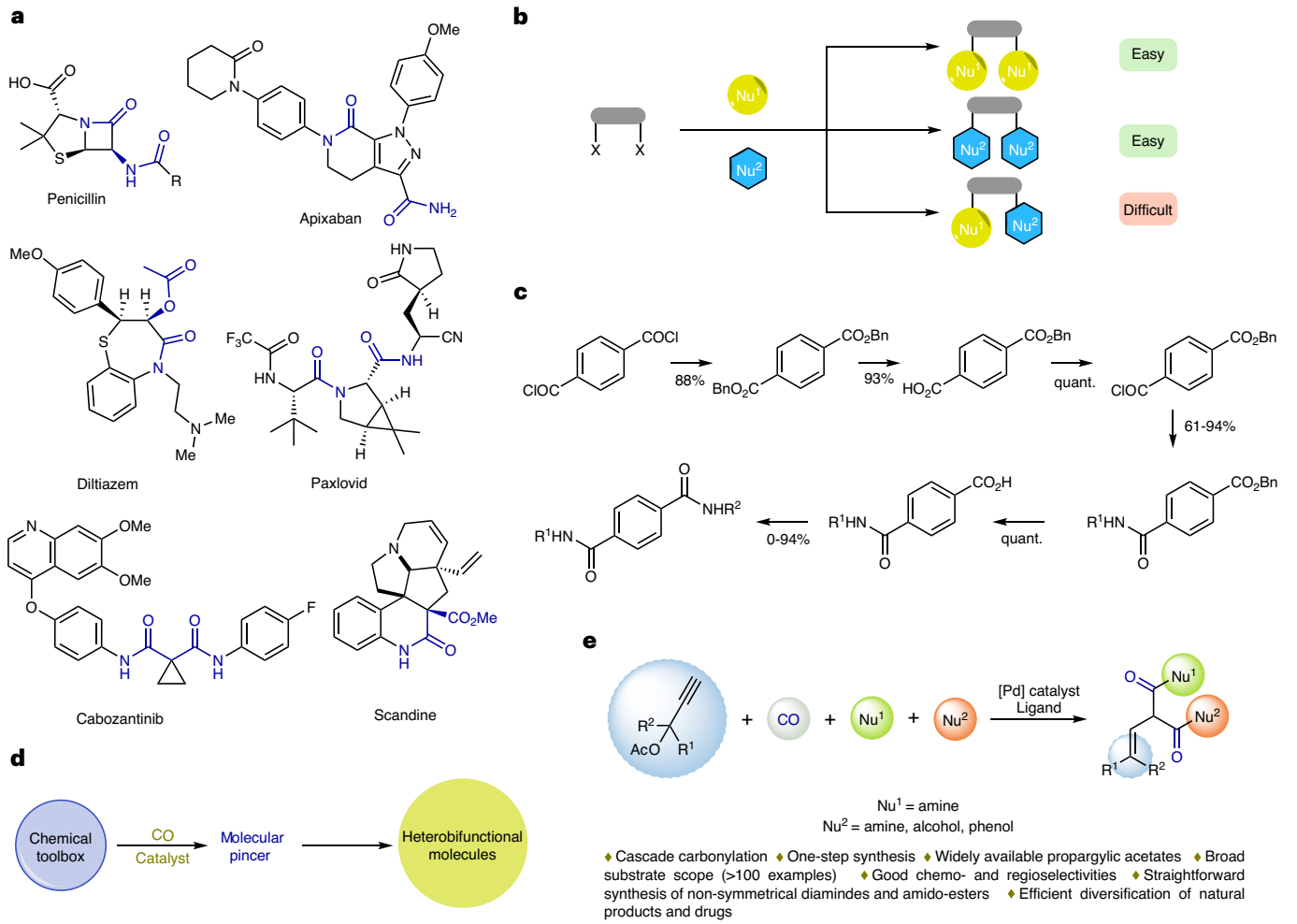


**Fig. 1 | Reaction design and development. a**, Selected examples of biologically active molecules and pharmaceuticals featuring diamide and amido-ester skeletons. **b**, Traditional ways of synthesizing non-symmetrical diamides **c**, An example for preparation of non-symmetrical terephthaldiamides, over six synthetic steps[19]. **d**, General concept for conversion of a chemical toolbox to heterobifunctional molecules through link chemistry. **e**, The method reported in the present study to access non-symmetrical diamides and amido-esters through dicarbonylation reactions.

fragments in a most efficient way; however, these methods make use of distinctly different molecules[23,24]. Inspired by this concept, we thought it would be appealing to develop a strategy for tethering two or more amines and/or alcohols selectively together with an appropriate molecular pincer as the cross-linking reagent (Fig. 1d). Such tethering of distinguished molecules, but with the same functional group, can be an efficient way to diversify chemical space[25]. As amino groups are omnipresent in pharmaceutically active compounds, their linkage by a molecular pincer can result in completely new biological activities[26–29].

To realize such transformations, the development of suitable linking reagents, which allow the selective connection of two different functional groups with similar reactivities, is crucial. As an extension to traditional link chemistry, which relies on high-throughput screening or iterative trial and error[25,29,30], we had the idea of selectively generating two different activated carboxylic acyl groups in situ via transition metal-catalysed carbonylation reactions (Fig. 1e), which are among the most important applications of industrial catalysis to produce a variety of bulk and fine chemicals[31–38].

## Results

### Reaction design and catalyst development

Recently, we demonstrated the usefulness of palladium (Pd)-catalysed mono- and dicarbonylation reactions of propargylic alcohols for the preparation of diverse heterocyclics. Notably, depending on the phosphine ligands, different reaction pathways can be controlled[39–41]. Thus, we had the idea that such transformations offer a unique way to utilize previously unexplored double carbonylations to tether amines using propargylic acetates as a molecular toolbox of the linkers. Challenges associated with such transformation are: (1) the catalyst must promote the different carbonylation reactions on the substrate; (2) the first amide bond must be formed selectively, despite the similar reactivities of diverse nucleophiles; and (3) side reactions such as monocarbonylation, isomerization and hydroamination must be suppressed too. Finally, it is worth mentioning that, specifically in the presence of amines and related substrates required for the synthesis of carboxamides, contradictory reactivity (acidic metal hydrides versus basic aliphatic amines) needs to be tolerated[42]. Thus, it is not surprising that, to the best of our knowledge, no such process has yet been reported. At the start, we selected 2-phenylbut-3-yn-2-yl acetate, **1a**, as a stable precursor for the molecular pincer. Its reaction with hexylamine, **2a**, and *N*-methylaniline, **3a**, was selected as a model system for connecting aliphatic and aromatic amines together and thereby providing an array of non-symmetrical malonamides (Table 1). Notably, malonamides are frequently found in retropeptidic derivatives, with the amide moiety serving as a functional linker to connect two fragments[10,16]. To control the chemo- and regioselectivity in this highly complicated reaction network, the selection of the catalyst system is crucial[31–36,39,43,44]. Thus, at the start of our study, we tested different mono- and bidentate phosphine

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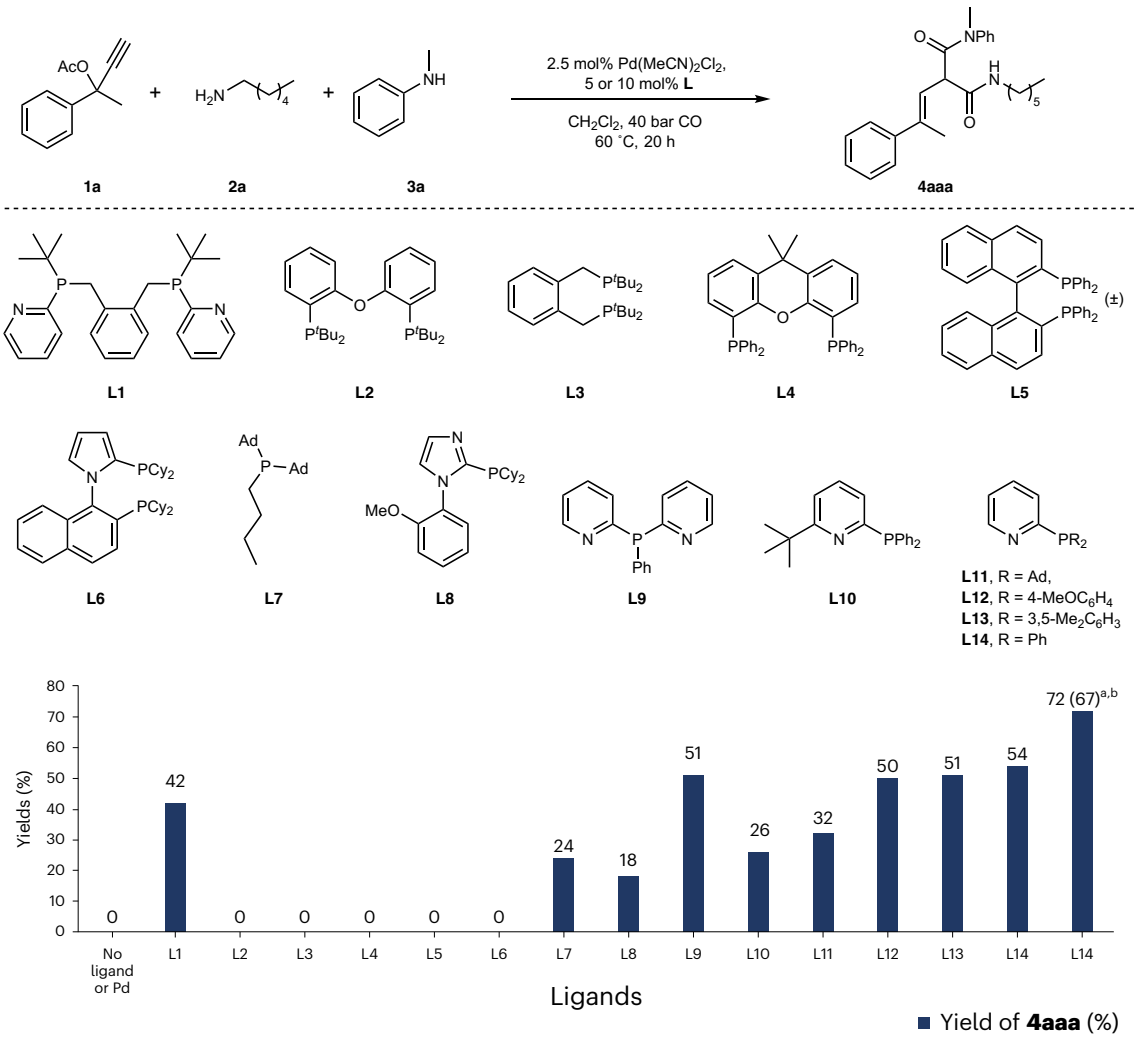
**Table 1 | Ligand optimization for Pd-catalysed dicarbonylation of 2-phenylbut-3-yn-2-yl acetate, 1a**




Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), **3a** (0.2 mmol), $Pd(MeCN)_2Cl_2$ (2.5 mol%), bisphosphine ligand (5.0 mol%) or monophosphine ligand (10.0 mol%), CO (40 bar), $CH_2Cl_2$ (2.0 ml), 20 h at 60 °C. The yields of products were determined by crude $^1H$ NMR spectroscopic analysis using dibromomethane as the internal standard. [a]**2a** (0.3 mmol), **3a** (0.3 mmol). [b]Isolated yield. Ac, acetyl; Ad, adamantyl; Cy, cyclohexyl.

ligands (10 and 5 mol%, respectively) in the carbonylation of **1a** in the presence of 2.5 mol% $Pd(MeCN)_2Cl_2$, dichloromethane (solvent) and 40 bar CO at 60 °C (Table 1). As expected, no reaction occurred without ligand or Pd present. In the presence of our recently developed ligand **L1** (LIKATphos)[45] with 2-pyridyl-*tert*-butylphosphino groups, which proved to have unique reactivity in alkoxy carbonylations, full conversion occurred with the desired non-symmetrical malonamide **4aaa** as the main product (42% yield). Evaluating other commonly used bisphosphines, **L2**–**L6**, either provided complex reaction mixtures or did not give this product at all. Surprisingly, among the monophosphine ligands, **L7**–**L9** and **L9** gave an improved yield of **4aaa** (51%). Consequently, we studied the effect of analogous ligands **L10**–**L14** with different steric and electronic properties. When diphenyl(2-pyridyl)-phosphine, **L14** (ref. 46), was applied, the yield of this non-symmetrical dicarbonylation product reached 54%. The effectiveness of **L14** and related ligands is explained by the pyridine substituent on the phosphorous atom, which improved the rate of nucleophilic attack on the intermediate palladium acyl complex[39–41,45]. By variation of reaction parameters (catalyst precursor, temperature, pressure, etc.) in the presence of **L14**, the yield of **4aaa** was improved to 72% and only small amounts (<10%) of symmetrical diamides were formed (Supplementary Tables 1–8).

## Mechanistic investigations

To understand the selectivity of this reaction in more detail, the dicarbonylation of **1a** with benzylamine, **2b**, and *N*-methylaniline, **3a**, was monitored under standard catalytic conditions; **2b** was used as a coupling partner because of the convenient characterization of the corresponding intermediates. As shown in Fig. 2a, the target product **4aba** was formed in 53% yield, whereas many species including allenoic amide **Int 1**, allylic amine **Int 2** and dienamide **Int 3** could be detected by $^1H$ nuclear magnetic resonance (NMR) spectroscopic analysis. At first, **1a** is converted into the allenoic amide, **Int 1**, which achieved a maximum yield of 42% after 45 min. Soon after, the starting material, **1a**, is fully converted and formation of allenoic amide, **Int 1**, allylic amine, **Int 2**, and dienamide, **Int 3**, took place. Then, **4aba** is generated along with the consumption of the reaction intermediates **Int 1**, **Int 2** and **Int 3**. After 8 h, the reaction is almost complete (Fig. 2b).

Next, control experiments were performed using **Int 1** and **Int 2** as starting materials (Fig. 2c). Indeed, the target compound **4aba** was produced in 42% and 53% yield, respectively, under standard conditions, which confirmed that **Int 1** and **Int 2** are active reaction intermediates in the overall process. Based on these findings and previous mechanistic studies of Pd-catalysed carbonylations[35,39–41,47–51], we propose the following main reaction pathway (Fig. 2d): initially, the stable $Pd^{II}$ salt could

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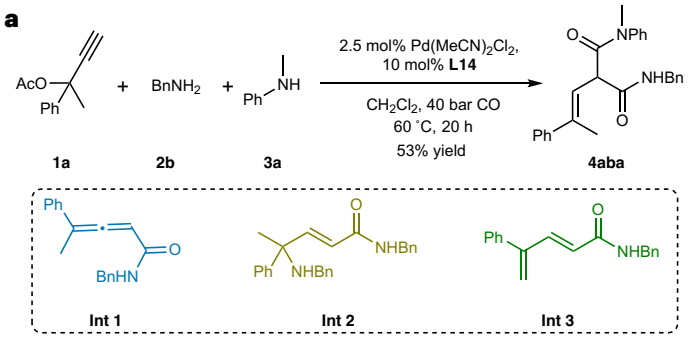


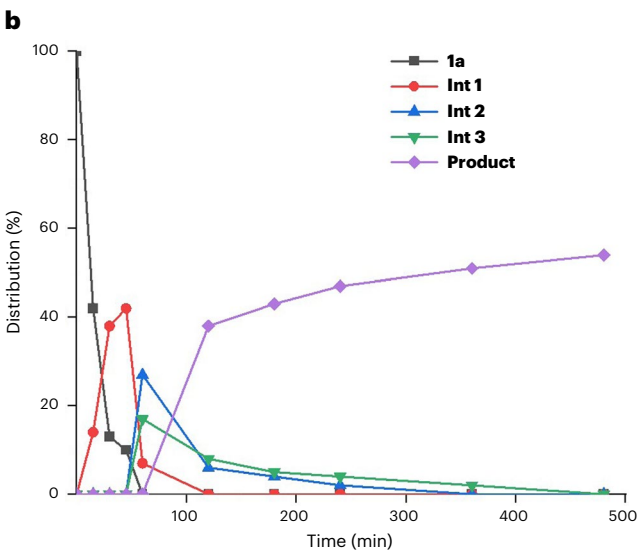


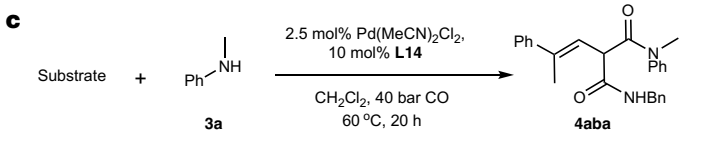


| Substrate | Yield of **4aba** (%) |
|---|---|
| **Int 1** | 42 |
| **Int 2** | 53 |

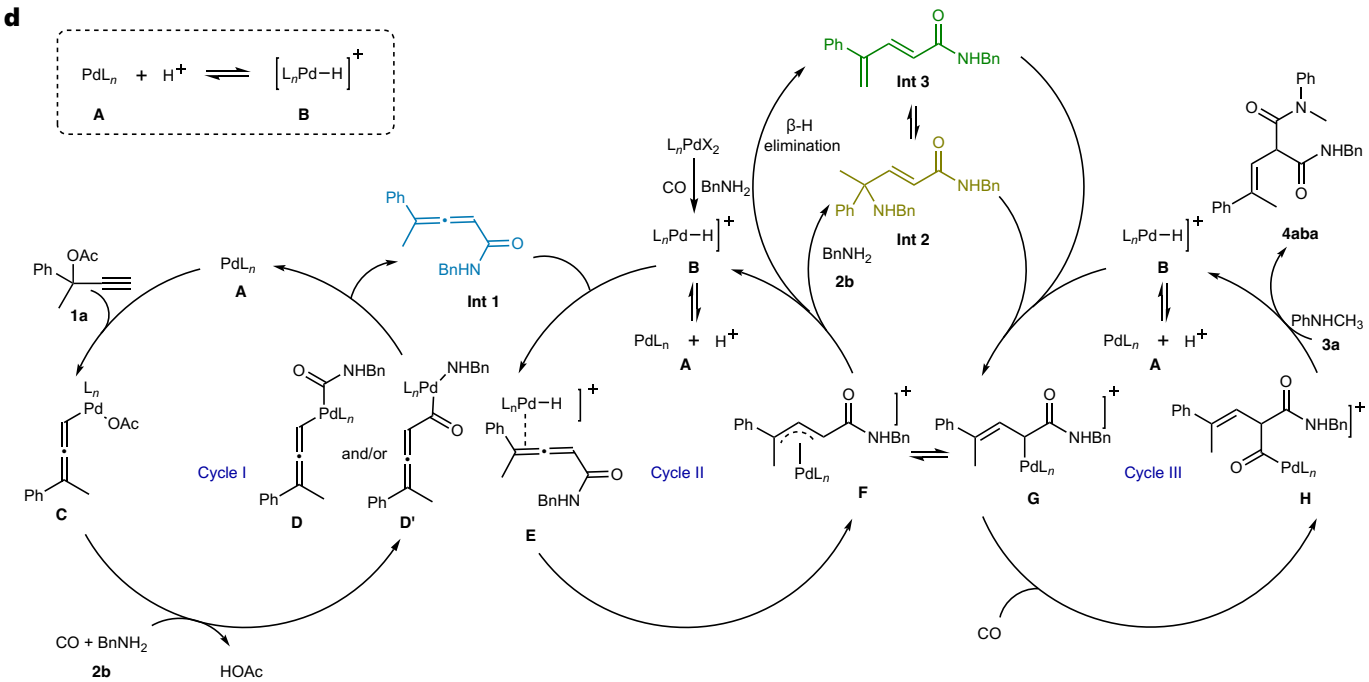


**Fig. 2 | Kinetic study, control experiments and proposed catalytic cycle.** **a**, Main species isolated from Pd-catalysed carbonylation of **1a** with **2b** and **3a**. **b**, Kinetic monitoring of intermediates over time by $^1$H NMR spectroscopic analysis. **c**, Control experiments: **Int 1** and **Int 2** were transformed to **4aba**, which confirmed that **Int 1** and **Int 2** are active reaction intermediates in the overall process. **d**, Proposed mechanism for a catalyst-controlled strategy to deliver malonamide, **4ab**. The reaction of **1a** and **2b** affords **Int 1**. **Int 1** reacts with Pd and H affords $\pi$-allyl-palladium intermediate **F**, which undergoes equilibrium to give σ-palladium complex, **G**, β-H elimination to give **Int 3** and amination to give **Int 2**. Subsequent transformations of **G**, **Int 2** and **Int 3** lead to **4aba** and turn over the catalytic cycle. Bn, benzyl.

be in situ reduced to give the $Pd^0$ phosphine complex **A** in the presence of an excess amount of ligand[52,53]. In the presence of $Pd^{II}$, **2b** and high pressure of CO, the corresponding urea and cationic palladium hydride species, **B**, were formed, subsequently establishing an equilibrium with species **A**[49]. In cycle **I**, $Pd^0Ln$ **A** will undergo $S_N2'$-type oxidative addition with propargylic acetate **1a** to give the allenylpalladium intermediate **C**, which reacts with CO and benzylamine, **2b**, to afford the carbonylation intermediates **D** or **D'**. Subsequently, reductive elimination affords the allenoic amide **Int 1** and regenerates the catalyst. **Int 1** is supposed to form complex **E** and subsequent olefin insertion regioselectively forms the $\pi$-allyl-palladium intermediate **F**. This species is in fast equilibrium with the corresponding σ-palladium complex **G**. Finally, CO insertion and aminolysis lead to the desired product, **4aba**. **F** is also prone to go through β-H elimination to form dienamide, **Int 3**, and amination to form allylic amine, **Int 2**.

Besides the possible balance between **Int 2** and **Int 3**, further reaction of the intermediates and Pd gives the σ-palladium complex **G**. In the same catalytic process, **4aba** is produced according to cycle III.

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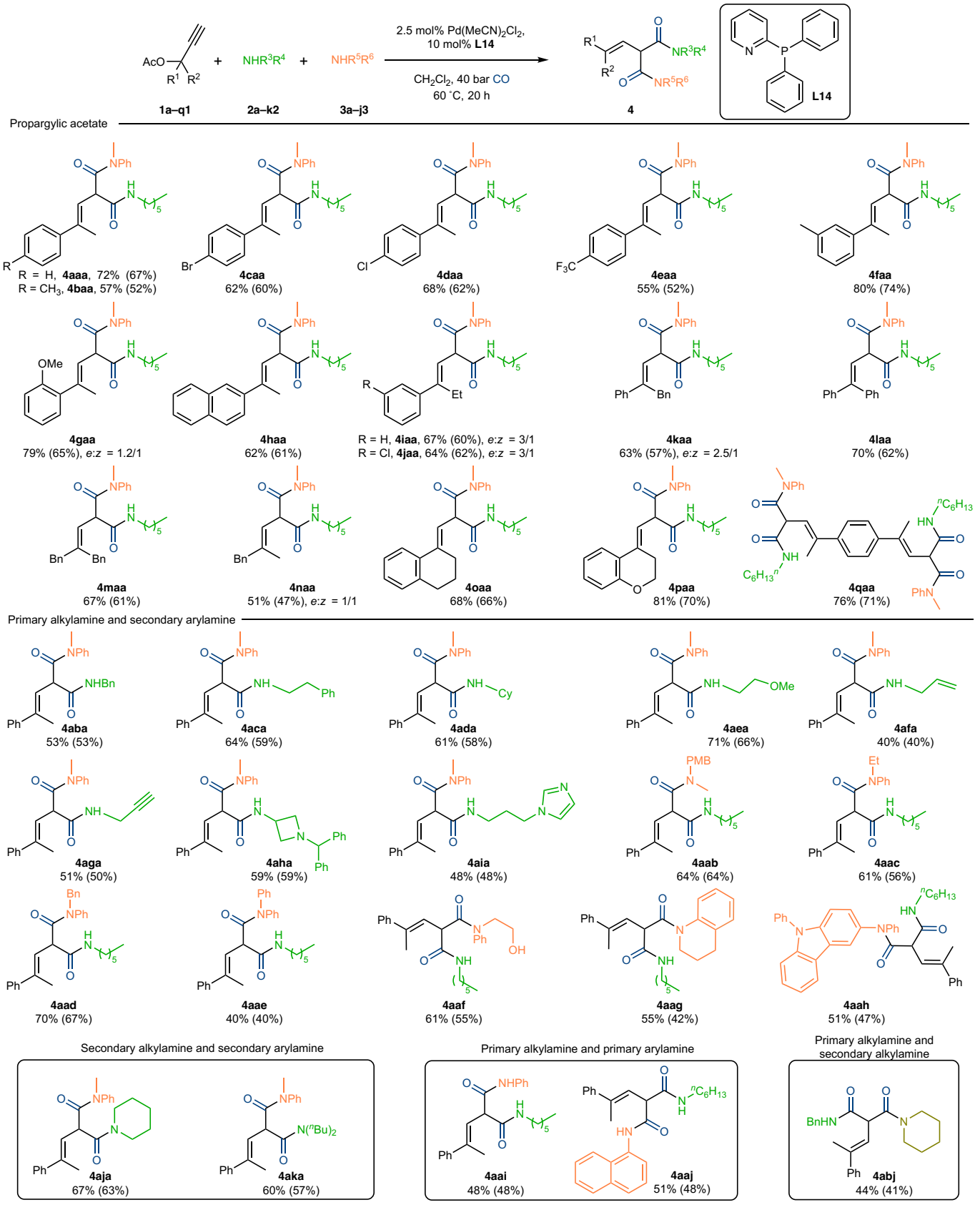
**Table 2 | Selective synthesis of non-symmetrical malonamides by Pd-catalysed carbonylation of propargylic acetates and amines**




Standard reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), **3** (0.3 mmol), $Pd(MeCN)_2Cl_2$ (2.5 mol%), **L14** (10 mol%), $CH_2Cl_2$ (2.0 mL), CO (40 bar), 20 h at 60 °C. Isolated yields are given within parentheses. $^1H$ NMR spectroscopic yields (values before parentheses) and z/e-selectivities of **4** were determined by crude $^1H$ NMR spectroscopic analysis using dibromomethane as the internal standard. Unless otherwise noted, the e:z ratio is >20:1 in all cases.

The selective formation of the non-symmetrical diamides is controlled by both the reactivity of the nucleophile and the ligand effect. The more reactive nucleophile reacts with the initially formed Pd complex **C**, whereas the second amine undergoes amination of acyl palladium complex **H**. Deprotonation of the second amine by the built-in base of the ligand allows an efficient nucleophilic attack on the acyl palladium[45].

## Substrate scope

With suitable conditions established for the model reaction, we examined the generality of this cascade, non-symmetrical, dicarbonylation process with respect to propargylic acetates as a molecular toolbox of tethering reagents. As shown in Table 2, diverse non-symmetrical malonamides can be conveniently prepared in the presence of the optimal catalytic system. Acetophenone analogues, **1b**–**1g**, and 2-acetonaphthone-derived propargylic acetate, **1h**, worked well to give the corresponding products **4baa**–**4haa** in 52–74% yields smoothly. In addition, other alkylated substrates led to the corresponding malonamides, **4iaa**–**4kaa**, in 57–62% yields with 2.5/1–3/1 selectivities. When 1,1-diphenylprop-2-ynyl acetate, **1l**, and **1m**–**1n** bearing benzyl and different alkyl groups were subjected to the optimized conditions, good activities and selectivities (47–62% yield) were achieved too. Furthermore, cycloalkyl-based propargylic acetates **1o**–**1p** can be transformed to the corresponding product **4oaa**–**4paa** in 66–70% yields. It is interesting that the highly functionalized product **4qaa** was obtained directly in 71% yield by multiple carbonylations of **1q**.

Next, we examined the general scope of the four-component process with respect to the reactivity of amines. Carbonylation reactions of **1a** with alkylamines and arylamines were performed in moderate-to-good yields. As shown in Table 2, primary alkylamines bearing alkyl chain (**2b** and **2c**), carbon ring (**2d**), functionalized groups (**2e**, **2f** and **2g**), heterocyclics (**2h and 2i**) and secondary alkylamines (**2j and 2k**) were all suitable partners in the reaction and gave the corresponding malonamides in 40–66% yields. Furthermore, diverse anilines (**3b**–**3j**), including the ones containing hydroxyl group (**3f**), heterocyclic motifs (**3g**) and hindered substituent (**3h**), underwent the desired transformation smoothly and the respective diamides **4aab**–**4aaj** were obtained in 40–67% yields. Notably, the more challenging combination of benzylamine (**2b**) and piperidine (**2j**) also worked selectively for this reaction, resulting in the formation of malonamide, **4abj**.

Tethering with proper linker chemistry provides new scaffolds for improved drug development[26,29]. Therefore, the combination of molecular pincer molecules with natural products or other biologically relevant molecules as reaction components offers many opportunities for the advancement of prodrug design. To showcase the applicability of the catalyst system to medicinal and complex organic chemistry, further functionalization of the molecular pincers was studied. As shown in Table 3, various functionalized primary alkylamines such as amino acid esters **2l** and **2m**, geranylamine (**2n**), oleylamine (**2o**), tryptamine (**2p**), myrtanylamine (**2q**), atorvastatin intermediate (**2r**), leelamine (**2s**), amlodipine (**2t**) and mexiletine (**2u**) were linked smoothly by carbonylation of **1a** and **3a** to the corresponding malonamides, **4ala**–**4aua**, in 40–63% yields. Numerous drugs or their derivatives containing secondary alkylamines (donepezil-related amine, **2v**, norquietapine, **2w**, buspirone-related amine, **2x**) as well as primary arylamines (vilazodone-related amine, **3k**, aminoglutethimide, **3l**) can be used in this multicomponent cascade process to furnish **4ava**–**4aal** in 47–64% yields in one step. The selective formation of **4ajt** in the presence of piperidine, **2j**, and amlodipine, **2t**, was also achieved despite their similar reactivities. The presented catalyst system is also well suited for generation of heterobifunctional compounds by bridging distinguished complex fragments or pharmacophores within one molecule. More specifically, geranylamine, **2n**, and vilazodone-related amine, **3k,** were coupled with **1a** to afford **4ank** in 51% yield. Similarly, the exploration of nucleophiles such as atorvastatin intermediate, **2r**, and sterically hindered amine, **3h**, amlodipine, **2t**, atorvastatin intermediate, **2r**, and aminoglutethimide, **3l**, showed that medicinally relevant molecules, **4arh, 4atl** and **4arl**, can be constructed in an efficient and selective manner, indicating the possibility of expanding the existing synthetic toolbox for chimeric molecule modification.

Amides are one of the most prolific moieties in pharmaceutical molecules, agrochemicals and natural products (see above)[1–9]. Therefore, there has been continuous interest in developing new amides that contain additional functional groups. In this respect, specifically amides with ester groups seemed interesting to us. Analogous to diamides, established approaches for synthesizing amido-esters encounter limitations owing to the low tolerance of functional groups under the reaction conditions used[54]. We thought that the developed double carbonylation reactions could be extended to provide the corresponding amido-esters. Again, to the best of our knowledge, such double-selective carbonylations have not been reported. The intrinsic challenges of such transformations are the possibilities of also forming diamides and diesters apart from the desired amido-esters. Furthermore, potential side reactions of propargylic acetates, which contain an unsaturated triple bond and an activated acetoxy group, increase the complexity of the system. Nevertheless, the reaction of propargylic acetate, **1a**, benzylamine, **2b**, and methanol, **5a**, provided amido-ester **6aba** in 41% yield, together with the diaminocarbonylation product **S9** and monocarbonylation products **Int 1** and **S10** under the previously developed conditions in the presence of **L14** as ligand. More detailed investigations of the chemo- and regioselectivity of this reaction allowed an increase in the yield of **6aba** up to 65% (Supplementary Tables 9–14).

As shown in Table 4, acetophenone analogues **1b**–**d** and **1f** and 2-acetonaphthone-derived propargylic acetate, **1h**, can be also used as connecting reagents providing the corresponding products **6bba**–**6hba** in 53–70% yields. The use of ethyl and benzyl-substituted substrates, **1i** and **1k**, led to amido-esters **6iba** and **6kba** in 67% (*e*:*z* = 3.9:1) and 59% yield (*e*:*z* = 3.3:1), respectively. In addition, 1-diphenylprop-2-ynyl acetate, **1l**, and dialkyl-substituted propargylic acetates, **1r** and **1m**, delivered the desired products smoothly. Finally, malonamides **6oba** and **6pba** were produced in 59–67% yields, starting from cycloalkyl-based propargylic acetates **1o** and **1p**.

Besides secondary amines (**2k**, **2A** and **2j**), primary ones (**2a**, **2c**, **2d**, **2e**, **2n**, **2y** and **2z**) are also suitable, giving the corresponding amido-esters in 48–68% yields. In addition, a variety of alcohols can be employed in this four-component reaction. Simple primary alcohols including ethanol (**5b**), *n*-butanol (**5c**), cyclopropylmethanol (**5d**) and halogen-containing alcohols (**5e**), as well as less reactive secondary alcohol, **5f**, and cholesterol, **5g**, gave the desired products **6abb**–**6abg**. As an example of a phenol derivative, vitamin E, **5h** was shown to be a suitable substrate in this transformation and provided **6abh** in 47% yield.

Recently, there has been increasing interest in so-called chimeric or multitargeting molecules, whereby the first component targets a specific cell or biological function and the second component exerts a different pharmacological activity. A stable or cleavable linker connects these two modules of a chimaera[27,29]. In this respect, the presented methodology also permits the simultaneous incorporation of two or more pharmaceutical elements. As shown in Table 5, various complex amines and alcohols are tethered with **1a** as the precursor of the linking unit. More specifically, Pd-catalysed selective carbonylation of **1a** progressed well with furfurylamine **2B** and furfurylalcohol, **5i**, glycine ethyl ester, **2l**, and nerol, **5j**, furnishing products **6aBi** and **6alj**. Furthermore, combination of cholesterol, **5g**, with oleylamine, **2o**, or amlodipine, **2t**, led to the formation of **6aog** and **6atg**. Steroid hormones such as pregnenolone, **5k**, stanolone, **5l**, and dehydroepiandrosterone, **5m**, participated with amlodipine, **2t**, oleylamine, **2o**, myrtanylamine, **2q**, atorvastatin intermediate, **2r**, and leelamine, **2s**, in this transformation, providing the target products **6aok**–**6asm** in 52–66% yields. Finally, the linkage of atorvastatin intermediate **2r** with

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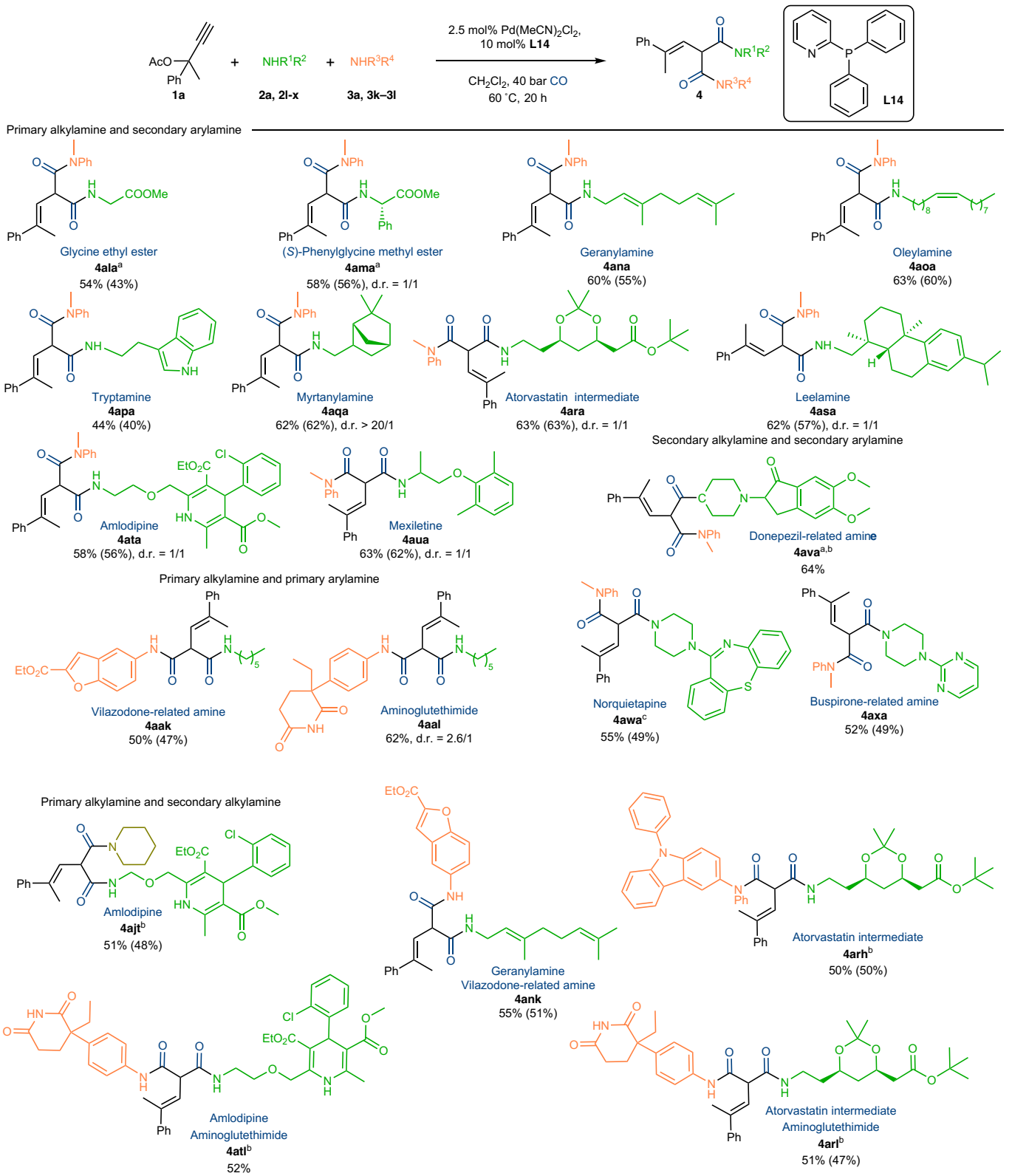
**Table 3 | Selective Pd-catalysed dicarbonylation for the synthesis of non-symmetrical malonamides with biologically relevant molecules**




Standard reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), **3** (0.3 mmol), $Pd(MeCN)_2Cl_2$ (2.5 mol%), **L14** (10 mol%), $CH_2Cl_2$ (2.0 ml), CO (40 bar), 20 h at 60 °C. Isolated yields are given within parentheses. NMR spectroscopic yields (values before parentheses) and *z*:*e*-selectivities of **4** were determined by crude $^1H$ NMR spectroscopic analysis using dibromomethane as the internal standard. Unless otherwise noted, the *e*:*z* ratio is >20:1 in all cases. [a]0.3 mmol amino acid ester hydrochloride and 0.3 mmol $Et_3N$ were used. [b]Isolated as mixture of diastereoisomers in an unknown ratio, the ratio could not be determined owing to overlapping signals in in the crude $^1H$ NMR spectra. [c]11-(Piperazin-1-yl)dibenzo[*b*,*f*][1,4]thiazepine dihydrochloride and 0.6 mmol $Et_3N$ were used.

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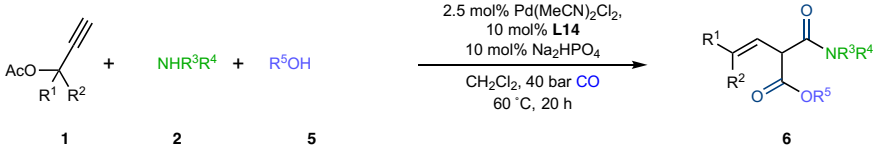
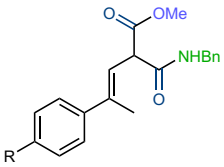
## Table 4 | Selective synthesis of amido-esters by Pd-catalysed dicarbonylation reactions

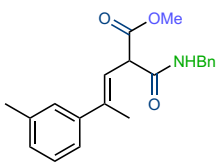



1 2 5 6

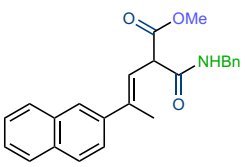
Propargylic acetate



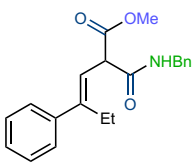
R = H, **6aba**, 65% (65%)
R = Me, **6bba**, 65% (65%)
R = Br, **6cba**, 53% (53%)
R = Cl, **6dba**, 59% (54%)



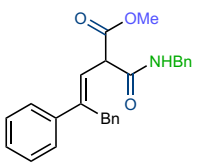
**6fba**
75% (70%)



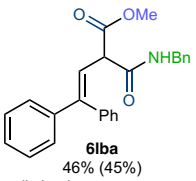
**6hba**
61% (55%)



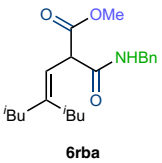
**6iba**
68% (67%), *e*:*z* = 3.9/1



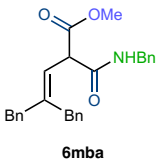
**6kba**
59% (59%), *e*:*z* = 3.3/1



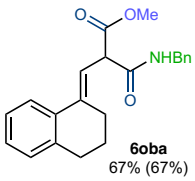
**6lba**
46% (45%)



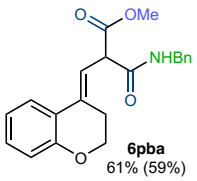
**6rba**
64% (61%)[a]



**6mba**
59% (55%)[a]

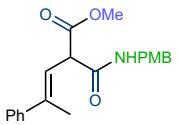


**6oba**
67% (67%)

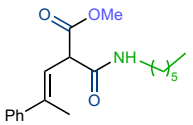


**6pba**
61% (59%)

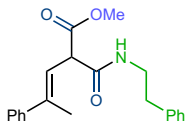
Primary alkylamine



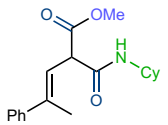
**6aya**
50% (50%)



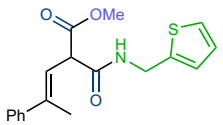
**6aaa**
63% (57%)



**6aca**
68% (68%)

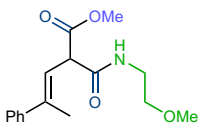


**6ada**
67% (63%)

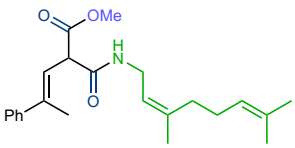


**6aza**
55% (48%)

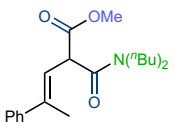
Secondary alkylamine



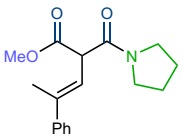
**6aea**
63% (61%)



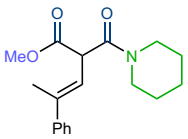
Geranylamine
**6ana**
58% (51%)



**6aka**
50% (49%)



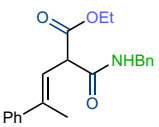
**6aAa**
70% (62%)



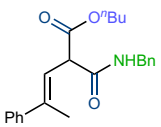
**6aja**
62% (62%)

Primary alcohol

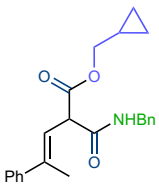
Secondary alcohol



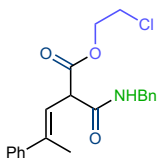
**6abb**
71% (64%)



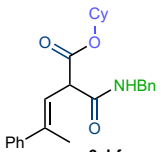
**6abc**
74% (63%)



**6abd**
57% (50%)

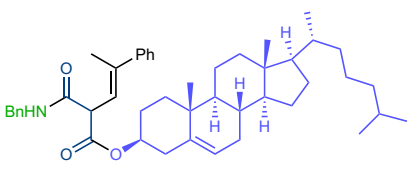


**6abe**
44% (44%)

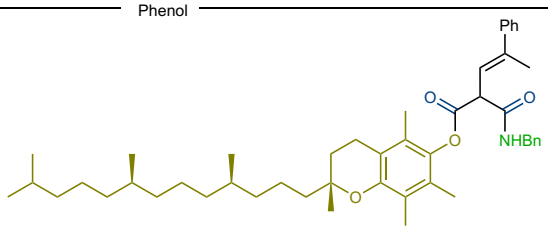


**6abf**
59% (55%)

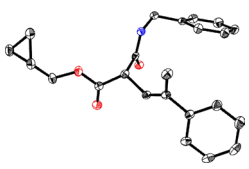
Phenol



Cholesterol
**6abg**[b]
57% (57%), d.r. > 20/1



Vitamin E
**6abh**[b]
48% (47%), d.r. > 20/1

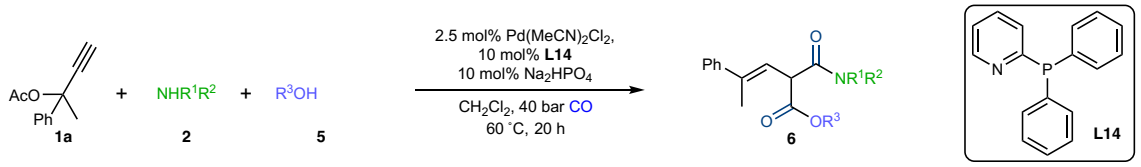


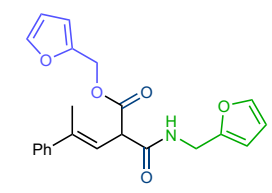
X-ray crystal structure of **6abd**[c]

Standard reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), **5** (0.6 mmol), $Pd(MeCN)_2Cl_2$ (2.5 mol%), **L14** (10 mol%), $Na_2HPO_4$ (10 mol%), $CH_2Cl_2$ (2.0 ml), CO (40 bar), 20 h at 60 °C. Isolated yields are given within parentheses. NMR spectroscopic yields (values before parentheses) and *z*:*e*-selectivities of **6** were determined by crude $^1H$ NMR analysis using dibromomethane as an internal standard. Unless otherwise noted, *e*:*z* > 20/1 in all cases. [a]**2** (0.3 mmol); **5** (0.3 mmol). [b]**5** (0.2 mmol). [c]Displacement ellipsoid plot (30% probability level) of one molecule of the asymmetrical unit of **6abd** (without H).

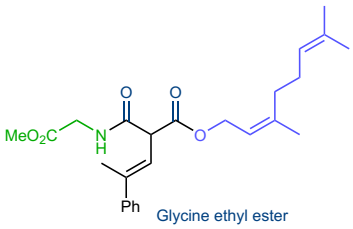
https://doi.org/10.1038/s44160-023-00411-6

**Table 5 | Pd-catalysed dicarbonylation for the synthesis of amido-esters with biologically relevant molecules**

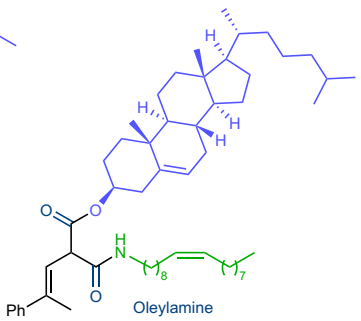


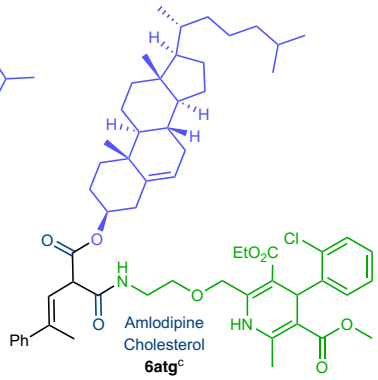
Furfurylamine
Furfurylalcohol
**6aBi**[a]
56% (50%)



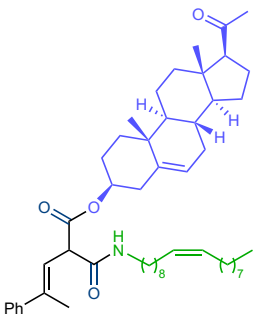
Glycine ethyl ester
Nerol
**6alj**[b]
39% (39%)



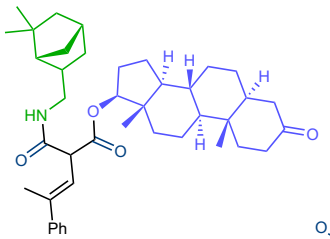
Oleylamine
Cholesterol
**6aog**[a,c]
60% (58%)



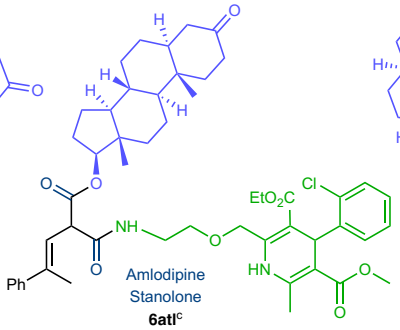
Amlodipine
Cholesterol
**6atg**[c]
45% (41%)



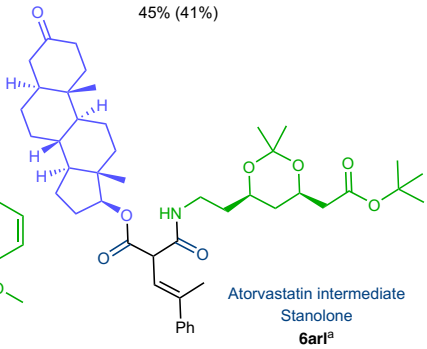
Oleylamine
Pregnenolone
**6aok**[a]
70% (65%), d.r. > 20/1



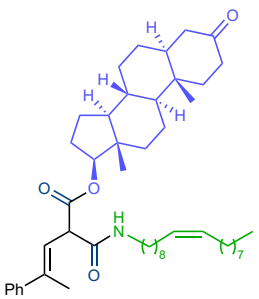
Myrtanylamine
Stanolone
**6aql**
58% (55%), d.r. = 1/1



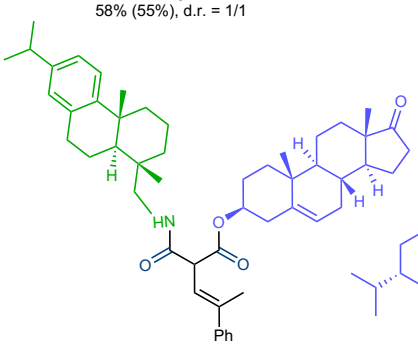
Amlodipine
Stanolone
**6atl**[c]
62% (60%)



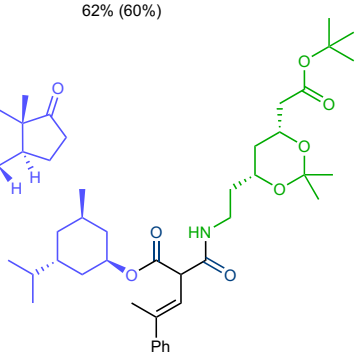
Atorvastatin intermediate
Stanolone
**6arl**[a]
65% (64%), d.r. = 1/1



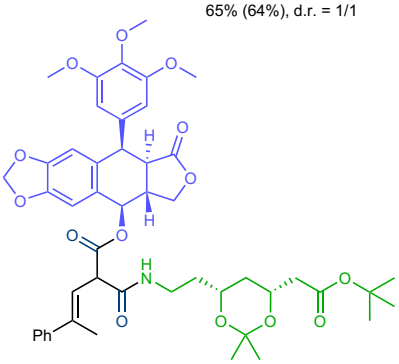
Oleylamine
Stanolone
**6aol**
52% (52%), d.r. = 1/1



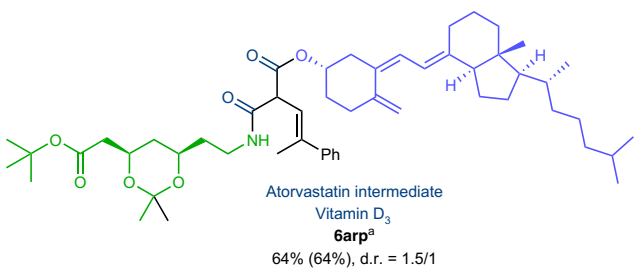
Leelamine
Dehydroepiandrosterone
**6asm**[a]
71% (66%), d.r. = 1/1



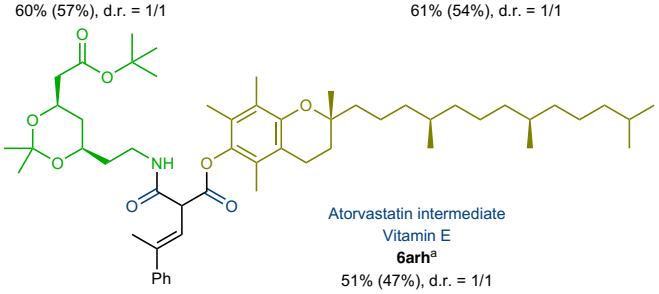
Atorvastatin intermediate
(–)-Menthol
**6arn**[a]
60% (57%), d.r. = 1/1



Atorvastatin intermediate
Podophyllotoxin
**6aro**[a]
61% (54%), d.r. = 1/1



Atorvastatin intermediate
Vitamin $D_3$
**6arp**[a]
64% (64%), d.r. = 1.5/1



Atorvastatin intermediate
Vitamin E
**6arh**[a]
51% (47%), d.r. = 1/1

Standard reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), **5** (0.2 mmol), $Pd(MeCN)_2Cl_2$ (2.5 mol%), **L14** (10 mol%), $Na_2HPO_4$ (10 mol%), $CH_2Cl_2$ (2.0 ml), CO (40 bar), 20 h at 60 °C. Isolated yields are given within parentheses. NMR spectroscopic yields (values before parentheses) and *z*:*e*-selectivities of **6** were determined by crude $^1H$ NMR spectroscopic analysis using dibromomethane as an internal standard. Unless otherwise noted, *e*:*z* > 20/1 in all cases. [a]**2** (0.3 mmol), **5** (0.3 mmol). [b]0.3 mmol amino acid ester hydrochloride and 0.3 mmol $Et_3N$ were used. [c]Isolated as mixture of diastereoisomers in an unknown ratio, the ratio could not be determined due to overlapping signals in in the crude $^1H$ NMR spectra.

(−)-menthol, **5n**, podophyllotoxin, **5o**, vitamin $D_3$, **5p**, and vitamin E, **5h**, was also achieved with this protocol, producing the corresponding amido-esters in 47–64% yields.

## Conclusions

In summary, we report a general and atom-efficient, one-step synthesis of non-symmetrical diamides or amido-esters by using either two different amines or amines and alcohols, respectively. The presented methodology permits tethering of diverse amines, alcohols and phenols together with molecular pincers, thereby enabling the synthesis of heterobifunctional compounds in a completely new way. The selective linking reagent, the molecular pincer, is generated in situ by Pd-catalysed carbonylation of convenient and stable propargylic acetates. By using different propargylic acetates, a toolbox of different linking reagents can be easily created. Mechanistic studies of the diamino- and amino-alkoxy carbonylation reactions suggest a sequential carbonylation process with allenoic amide, allylic amine and dienamide as major intermediates. The development of development of the $Pd(MeCN)_2Cl_2$/diphenyl(2-pyridyl)-phosphine catalyst system was crucial for controlling the selectivity in the complex reaction network. The presented chemistry offers new ways for diversification in chemical space and the generality is demonstrated in >100 examples. To the best of our knowledge, the prepared molecules shown in the present study have not been described before.

## Methods

### General procedure for carbonylation

A 4-ml screw-cap vial was charged with $Pd(MeCN)_2Cl_2$ (1.3 mg, 0.005 mmol) and ligand (0.02 mmol). The synthesis of **4aaa** was achieved by adding **1a** (0.2 mmol), **2a** (0.3 mmol), and **3a** (0.3 mmol); the synthesis of **6aba** was achieved by adding **1a** (0.2 mmol), **2b** (0.2 mmol), **5a** (0.6 mmol), and $Na_2HPO_4$ (0.02 mmol); and an oven-dried stirring bar. The vial was closed by a poly(tetrafluoroethylene)/white rubber septum (Wheaton 13 mm Septa) and a phenolic cap and connected to the atmosphere with a needle. Then, the vial was evacuated under vacuum and recharged with argon 3×. After $CH_2Cl_2$ (2.0 ml) was injected by syringe, the vial was fixed in an alloy plate and put into a Parr 4560 series autoclave (300 ml) under an argon atmosphere. At room temperature, the autoclave was flushed with carbon monoxide 3× and CO was charged to 40 bar. The reaction was heated to 60 °C and stirred for 20 h. Afterwards, the autoclave was cooled to room temperature and the pressure was carefully released. The reaction mixture was filtered through a short pad of celite and concentrated via rotary evaporation. Dibromomethane (34.6 mg, 0.2 mmol) was added into the reaction as an internal standard. A sample of the mixture was analysed by $^1$H NMR Spectroscopy. Pure product could be obtained by column chromatography on silica gel. Cautionary note: CO is harmful when breathed. Gas charging and releasing should be operated in a fume hood.

## Data availability

All the data generated or analysed during the present study are included in this article and its Supplementary Information. Crystallographic data for the structure reported in this article have been deposited at the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service, under deposition no. CCDC 2190217 (**6abd**). Copies of the data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures.

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## Author contributions

M.B. and Y.G conceived and designed the experiments. Y.G., W.H. and S.A. performed the experiments and analysed the data. A.S. performed the X-ray analysis. R.J. participated in the discussions and provided high-pressure infrastructure. M.B. and Y.G. prepared the manuscript with feedback from all authors.

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## Competing interests

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## Additional information

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