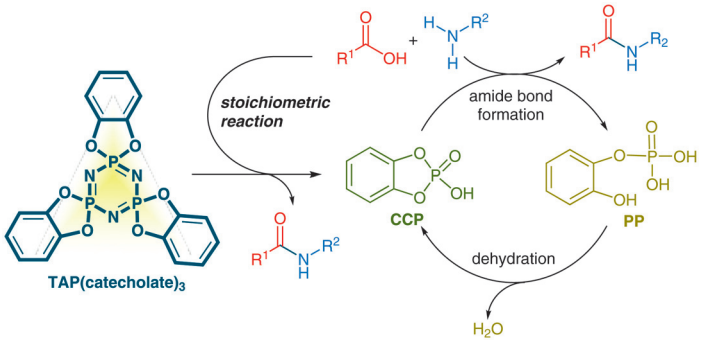
Synthesis F. S. Movahed et al. Special Topic

Tris(*o*-phenylenedioxy)cyclotriphosphazene as a Promoter for the Formation of Amide Bonds Between Aromatic Acids and Amines

Farzaneh Soleymani Movahed[a]
Dinesh N. Sawant[b]
Dattatraya B. Bagal[a]
Susumu Saito*[a,b]

[a] Graduate School of Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan
[b] Research Center for Materials Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan
saito.susumu@f.mbox.nagoya-u.ac.jp

Published as part of the Special Topic *Recent Advances in Amide Bond Formation*



Received: 24.04.2020
Accepted after revision: 04.06.2020
Published online: 06.07.2020
DOI: 10.1055/s-0040-1707174; Art ID: ss-2020-c0222-st

Abstract The atom-efficient formation of amide bonds has emerged as a top-priority research field in organic synthesis, as amide bonds constitute the backbones of proteins and represent an important structural motif in drug molecules. Currently, the increasing demand for novel discoveries in this field has focused substantial attention on this challenging subject. Herein, the degradable 1,3,5-triazo-2,4,6-triphosphorine (TAP) motif is presented as a new condensation system for the dehydrative formation of amide bonds between diverse combinations of aromatic carboxylic acids and amines. The underlying reaction mechanism was investigated, and potential catalyst intermediates were characterized using ^{31}P NMR spectroscopy and ESI mass spectrometry.

Key words amide bond formation, organophosphorus catalyst, dehydration, carboxylic acids, amines

Introduction

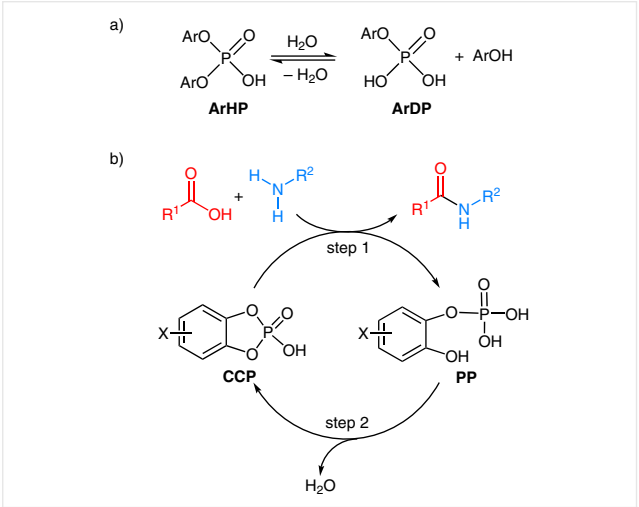
The amide bond is a key component in many biologically active compounds, natural products, and therapeutics, as well as in the food and agricultural industries.[1] In fact, 25% of all synthetic drugs contain amide units.[2] However, the condensation of carboxylic acids (CAs) and amines remains one of the most challenging transformations in organic synthesis, and 'amide formation avoiding poor atom economy reagents' has been selected as a top-priority research area in organic chemistry.[3]

In addition to direct amidation reactions between CAs and amines at high temperatures (e.g., >200 °C),[4] numerous low-temperature amidation strategies have been established, among which the application of coupling reagents [such as *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HATU), COMU®, and Oxyma®] has emerged as one of the most successful approaches.[5] The catalytic activation of CAs is an intriguing method that generally provides the desired amide bond with high atom economy at reasonably low temperatures (<100 °C).[6] A very recently published report by Yamamoto et al. introduced a novel strategy in which a substrate-directed Lewis acid tantalum catalyst and a stoichiometric amount of trimethylsilylimidazole were used for the activation of CAs; this method allows the synthesis of peptides at 45 °C without significant racemization.[7] Another noteworthy report by Arora et al. explored a selenium-based organocatalyst that demonstrated outstanding performance for solid-phase synthesis of oligopeptide, albeit on a relatively small scale.[8] Due to the paramount importance of developing catalytic and waste-free approaches, a multitude of dehydration catalysts has been presented in the literature as a possible solution for CA activation, most of which are based on boron.[6,9] Since the first report of arylboronic acid catalysts by Yamamoto et al.,[9a] many groups have reported boron-based systems for the amidation of CAs.[9] However, most of these reports have focused mainly on the catalytic synthesis of peptides or the amidation of aliphatic CAs,[6–11] with a few exceptions[10] that include our recent report of diboron catalysts.[12] Many recently developed catalytic amidations require the use of heavy transition metals. However, these materials are scarce, and often present environmental hazards and increased toxicity.[13] Accordingly, the use of earth-abundant, environmentally benign organocatalysts represents a desirable research target.

In addition to numerous organoboron catalysts, a variety of organophosphorus compounds have been introduced as stoichiometric dehydrative coupling reagents[14] based on the characteristic Lewis-acidity of the phosphorus(V) atom.[15] While these compounds can be considered as effective promoters of CA–amine condensation, they often suffer from low tolerance toward hydrolysis, and robust efficient organophosphorus catalysts that promote the formation of amide bonds remain elusive. One promising strategy to potentially overcome this drawback is the development of a

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

dehydrative catalytic cycle based on the simple interconversion of diaryl hydrogen phosphate (ArHP) and aryl dihydrogen phosphate (ArDP) by the addition and removal of water (Scheme 1a). The use of a cyclic phosphate would be expected to provide a more robust dehydrative cycle for the catalytic condensation of a CA and an amine (Scheme 1b).



Scheme 1 Working hypothesis of this study: (a) Interconversion between ArHP and ArDP via the addition or removal of water could lead to a dehydrative catalytic cycle. (b) The ideal catalytic cycle for the formation of amide bonds between CAs and amines via the catalytic interconversion of CCP and PP.

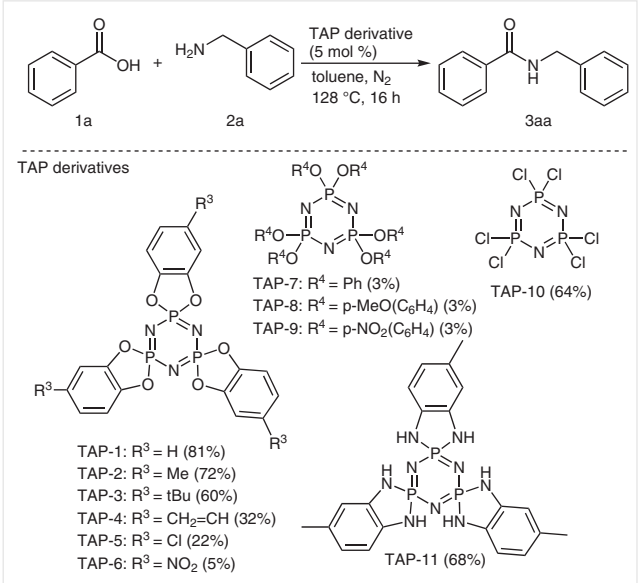
The proposed catalytic cycle (Scheme 1b) involves two main steps: First, the interaction of the CA with the ArHP catalyst catechol cyclic phosphate (CCP; in this specific case) yields the active ester species, which is immediately attacked by the amine in the reaction mixture (step 1). Second, detachment of the desired amide from the cycle and hydration of CCP leads to the open ArDP structure PP (pyrocatechol phosphate), which is converted back to the closed CCP structure upon azeotropic removal of H_2O (step 2). Based on these hypothetical considerations, we undertook an extensive search to find effective reaction conditions for the synthesis of CCP; however, several previously published studies have concluded that the direct isolation of CCP might be impracticable,[16] and accordingly, we targeted the in situ generation of CCP. As part of our continuous endeavor to employ 1,3,5-triazo-2,4,6-triphosphorine (TAP) derivatives as catalysts for dehydration reactions,[17] we report herein that TAP(catecholate)$_3$ [tris(*o*-phenylenedioxy)cyclotriphosphazene: TAP-**1**], which exhibits a high propensity to undergo hydrolysis under acidic or basic conditions,[18] serves as an effective precursor for the CCP/PP catalyst. An investigation into the underlying reaction mechanism clearly identified TAP-**1** as a practical precursor that both produces the catalyst and acts as a coupling reagent in the early stage of amide formation, which is followed by the CCP–PP catalytic cycle.

Results and Discussion

The uncatalyzed dehydrative amidation of aliphatic CAs and amines is well established,[11] while that of aromatic CAs is non-trivial.[12] Our initial aim was to find an effective and simple method to generate ArHP (CCP) or ArDP (PP), whose structural robustness could potentially be the key to successfully induce amide bond formation with aromatic CAs. According to detailed studies by Allcock, phosphazenes readily undergo hydrolysis under acidic or basic conditions, which results in the in situ generation of ArHP (CCP) derivatives.[18] Therefore, a series of TAP derivatives were selected as potential catalyst precursors and synthesized via a slightly modified literature procedure.[19] For instance, cyclic triphosphazene TAP-**1** was obtained as a white solid from the reaction between catechol and hexachlorophosphazene (TAP-**10**) in the presence of K_2CO_3. The purification was achieved by simple filtration, and, due to the high stability of the isolated compound, the white solid could be stored under ambient conditions for at least 6 months.

Optimization of the Reaction Conditions

As a model reaction, we chose the amide bond formation between benzoic acid (**1a**) and benzylamine (**2a**). To investigate the feasibility of our proposed strategy, a wide variety of phosphazene derivatives was examined in order to identify the most promising organophosphorus structure (Scheme 2). The best results were obtained for TAP-**1** (5 mol %) under azeotropic reflux (128 °C) for 16 hours. In other words, TAPs that provide CCP (PP) promotors (TAP-**1** to TAP-**6** and TAP-**11**) perform significantly better than those that form ArHPs (ArDPs) (TAP-**7** to TAP-**9**).



Scheme 2 Amide bond formation between **1a** and **2a** (0.5 mmol each; $[\mathbf{1a}]_0 = [\mathbf{2a}]_0$ = 71 mM) in the presence of different organophosphorus derivatives of TAP. Values in parentheses refer to the yield of the crude product **3aa** as determined by ^{1}H NMR analysis using 1,2,2,2-tetrachloroethane as the internal standard.

Table 1 Optimization of the Reaction Conditions for the Amide Bond Formation Between **1a** and **2a**[a]

Entry	Conditions				Yield (%)[b]
	$[\mathbf{1a}]_0 = [\mathbf{2a}]$ (mM)	Temp (°C)	Time (h)	TAP-**1** (mol %)	
1	71	128	16	5	81
2	100	128	16	5	73
3	50	128	16	5	45
4	33	128	16	5	43
5	25	128	16	5	41
6	71	144	16	5	63
7	71	100	16	5	30
8	71	85	16	5	22
9[c]	71	66	16	5	16
10[c]	71	25	16	5	0
11	71	128	24	5	82
12	71	128	10	5	60
13	71	128	5	5	36
14	71	128	16	0.5	10
15	71	128	16	1	19
16	71	128	16	2	35
17	71	128	16	10	87
18	71	128	16	15	84
19[d]	71	128	16	5	60
20[e]	71	144	16	5	42
21[f]	71	85	16	5	12
22[c,g]	71	66	16	5	10
23[c,h]	71	40	16	5	0
24[c,i]	71	35	16	5	0

[a] Unless otherwise specified, the reaction was performed using **1a** and **2a** (0.5 mmol each) under N_2.
[b] Crude yield of **3aa** determined by ^{1}H NMR spectroscopy using 1,1,2,2-tetrachloroethane as the internal standard.
[c] Molecular sieve was used (4 Å, 2.4 g/1 mmol).
[d] Under air.
[e] Solvent: *o*-xylene.
[f] Solvent: MeCN.
[g] Solvent: THF.
[h] Solvent: CH_2Cl_2.
[i] Solvent: Et_2O.

After identifying TAP-**1** as the most appropriate phosphazene skeleton, we shifted our attention to optimizing the reaction conditions (Table 1). To this end, various parameters affecting the reaction conditions were assessed. Among the different solvents explored, toluene exhibited the best performance (Table 1, entries 1 and 20–24) at the optimized initial concentration ($[\mathbf{1a}]_0 = [\mathbf{2a}]_0 = 71$ mM), and provided the desired amide **3aa** in 68 ± 13% crude yield (average of five runs).

Then, the reaction temperature was varied. As expected, azeotropic reflux (128 °C, Table 1, entry 1) is crucial for the removal of water, and the highest yield of **3aa** was achieved under this condition (entries 1 vs 6–10). The maximum performance of the catalyst was achieved within a reasonable timeframe (16 h; entries 1 vs 11–13). Next, the TAP-**1** loading in toluene ($[\text{TAP-}\mathbf{1}]_0 = 3.57$ mM) was varied at azeotropic reflux at 128 °C (entries 1 vs 14–18), and 5 mol% of TAP-**1** was found to be sufficient to provide **3aa** in more than 80% yield. Finally, the employment of an inert atmosphere proved to have a significant effect on the amidation performance. The presence of air had a detrimental effect on this system (entry 19), decreasing the yield of **3aa** from 81% to 60%. This observation is consistent with previously reported results that described CCP as being highly sensitive to atmospheric conditions.[16]

Reaction Scope and Limitations

The substrate generality of this system with respect to aromatic CAs was investigated using the optimized conditions and TAP-**1** (5 mol%) (Scheme 3). The coupling of CAs **1a–p** with **2a** was successful in all cases. In particular, CAs that bear electron-withdrawing or electron-donating groups produced the corresponding amides in consistently high yields, with negligible differences (**3aa–pa**). It is worth noting here that *N*,*N*-dimethyl-substituted benzoic acid **1i**, which is scarcely soluble in nonpolar solvents, underwent the reaction effectively in polar chlorobenzene, albeit that the temperature had to be elevated slightly. In contrast, poor reactivity of **1i** was observed using our recently developed diboron catalysts.[12] Screening of the amine scope revealed that the secondary amines **2e** and **2g** also underwent condensation under these conditions in high yield (**3ae**: 87%; **3ag**: 70%). In contrast, the reaction of the aromatic amine aniline (**2i**) with **1a** afforded **3ai** in only 20% yield. Aromatic amines are relatively poor nucleophiles; therefore, the nucleophilic attack of **2i** on the activated CA can be expected to be ineffective. Sterically more hindered amines **2d** and **2f** are also poor substrates under the applied conditions, providing **3ad** and **3af** in low yield. To investigate the possibility of forming amide bonds using C-protected-α-amino acids, L-tryptophan derivative **2j** was used as the amine, and the desired amide **3aj** was isolated in 32% yield with a slight loss of optical purity.

Mechanistic Study

The mechanism of our system was explored through constant monitoring using ^{31}P NMR spectroscopy, ESI mass spectrometry, and the yield curve of the products during the reaction procedure (Figure 1a). The amidation between **1a** and **2a** was designated as the model experiment. To obtain the best insights from the ^{31}P and ^{1}H NMR data, **1a** and **2a** (3 mmol each) were reacted in the presence of 5 mol % of TAP-**1** under azeotropic reflux (128 °C) ($[\mathbf{1a}]_0 = [\mathbf{2a}]_0 = 300$ mM). Every 2 hours, an aliquot was removed from the reaction mixture under an inert atmosphere (flowing N_2), and

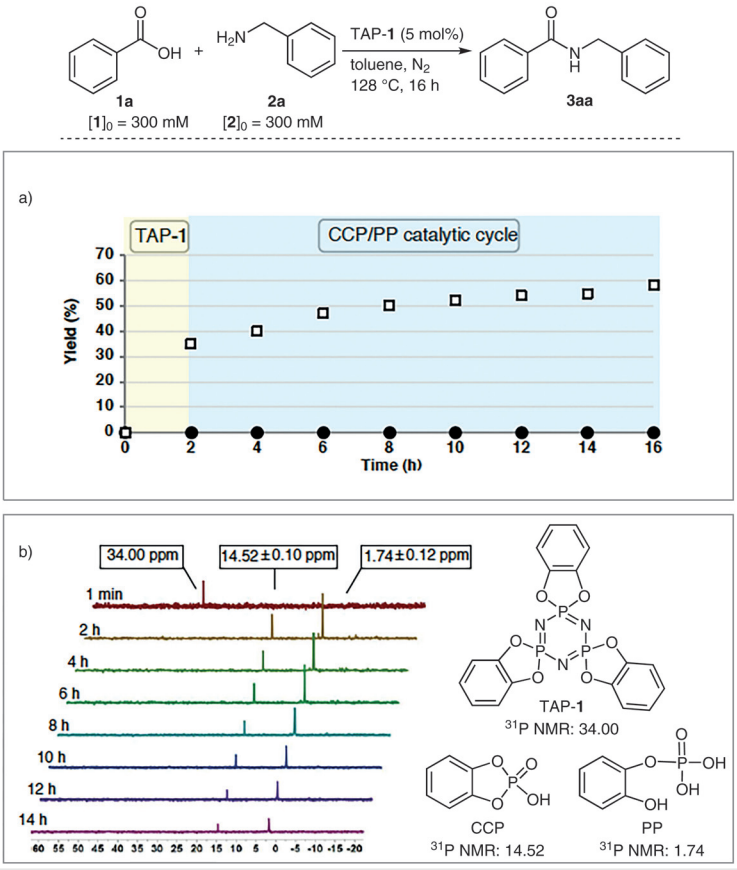
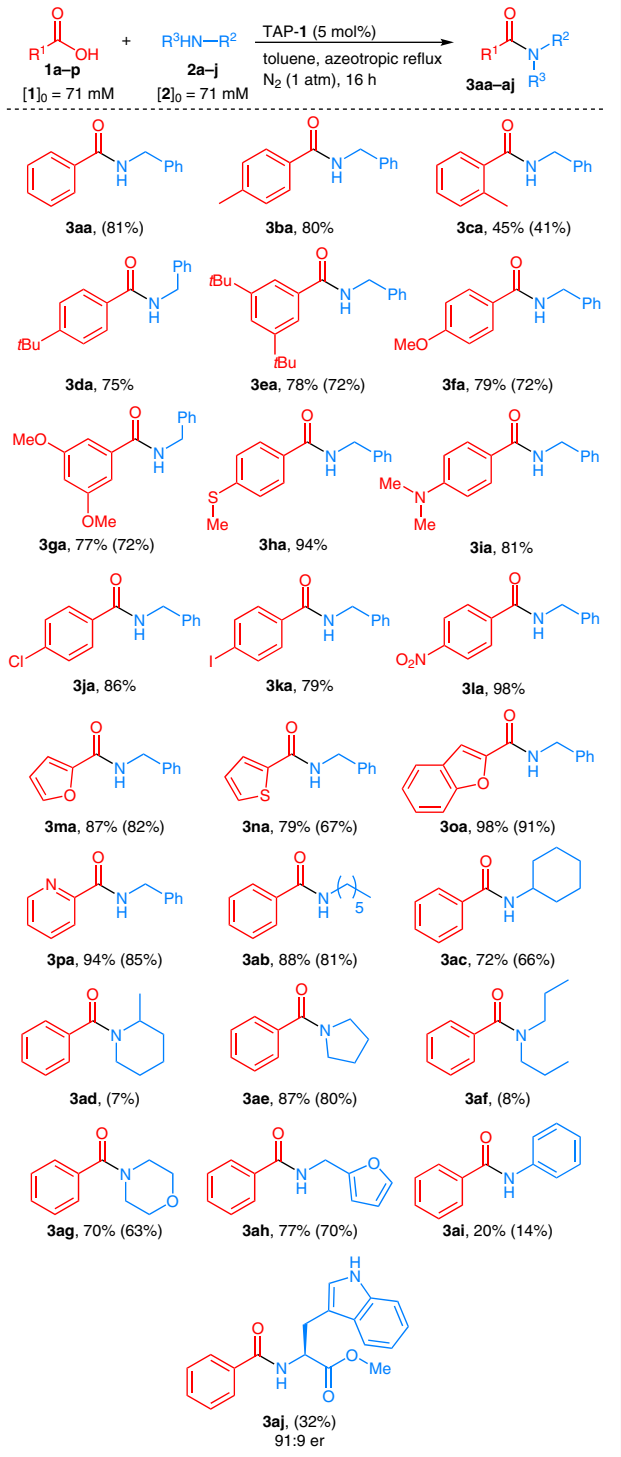


Figure 1 (a) Plot of the time-dependent yield of **3aa** during the reaction of **1a** and **2a** with (□) or without (●) TAP-**1** (5 mol %) (crude yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard). The sampling times were consistent in a) and b). (b) Stacked ^{31}P NMR spectra for the reaction between **1a** and **2a** (2 h intervals).

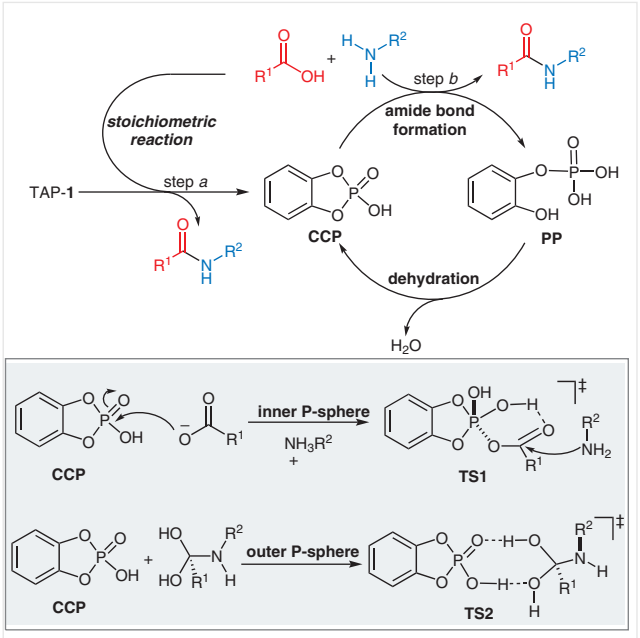
all the thus obtained samples were analyzed using ^{31}P and ^{1}H NMR spectroscopy as well as ESI mass spectrometry. Due to the instability of the catalyst CCP, the ^{31}P and ^{1}H NMR spectra were measured under N_2 gas (using screw-cap NMR tubes) to ensure the reliability of the data. The ^{31}P NMR results revealed that the total conversion of TAP-**1** occurred within 30 minutes of reaction, with two new signals appearing at 14.52 ± 0.10 ppm and 1.74 ± 0.12 ppm (Figure 1b).

To further identify these compounds, ESI mass spectra were recorded. As expected, CCP (ESI-MS $[M - H]^-$ calcd: 170.9853; found: 170.9869) was generated during the degradation of TAP-**1**, along with PP (ESI-MS $[M - H]^-$ calcd: 188.9958, found: 188.9974). Apart from a very small signal, which was tentatively assigned to phosphoric acid (H_3PO_4) that was consistently observed after ca. 8 hours of reaction and suggested the partial decomposition of CCP or PP to H_3PO_4 as a side reaction, other species were not observed by either ^{31}P NMR spectroscopy or ESI-MS, indicating that the transformation of TAP-**1** proceeded rapidly and efficiently. The ^{1}H NMR data recorded throughout the reaction were used to plot the yield curve (Figure 1a). As illustrated in Figure 1a, the reaction did not provide the desired amide bond under the standard conditions in the absence of TAP-**1**, whereas the addition of 5 mol % of this precursor promoted the reaction. During the reaction timeframe, the ^{31}P NMR peaks related to CCP and PP remained intact; moreover, the existence of these compounds was confirmed by ESI-MS measurements upon each sampling. Based on these data, we would like to propose the catalytic cycle as a plausible mechanism (Scheme 4).

As shown in Scheme 4, the catalyst precursor TAP-**1** acts as a stoichiometric reagent for the dehydrative coupling between the CA and the amine, and subsequently degrades completely into CCP upon reaction with the resulting H_2O. Following the generation of CCP, the catalytic cycle commences with CCP as the catalyst; the reaction of CCP with CA or an intermediate derived from a CA–amine adduct (step *b*) leads to the corresponding activated ester, which reacts with the amine via **TS1** (inner P-sphere mechanism) or directly forms **TS2** (outer P-sphere mechanism). In the case of **TS1**, a nucleophilic attack of the amine on the activated ester yields the desired amide and PP. In the final step, the concomitant removal of water from the PP structure



Scheme 3 Substrate scope. *Reagents and conditions*: Unless otherwise specified, the reaction was performed using **1** and **2** (0.5 mmol each) with TAP-**1** (5 mol %) in toluene for 16 h at a heating bath temperature of 128 °C. ^{1}H NMR yields of the crude mixtures using 1,1,2,2-tetrachloroethane as the internal standard are given (isolated yields in parentheses). For **3ia** and **3la**, PhCl was used as the solvent at 133 °C for 16 h.



Scheme 4 Overview of the mechanism of the 'stoichiometric TAP'-promoted amidation reaction (step *a*), followed by the catalytic CCP–PP interconversion cycle for the amidation. In step *b*, at least two transition states, **TS1** and **TS2**, are possible.

regenerates CCP, thereby completing the catalytic cycle. Due to the instability of CCP, the use of an inert reaction atmosphere, such as N_2, is crucial. To demonstrate the conversion of CCP to PP, a small portion of the reaction mixture was subjected to ^{31}P NMR analysis, which confirmed the presence of the CCP signal. This sample was subsequently exposed to air (containing moisture) for 12 hours. The ^{31}P NMR spectrum of the resulting sample did not contain any peak related to CCP; instead, PP was the only signal observed.

Conclusion

We have demonstrated a new catalytic system based on 1,3,5-triazo-2,4,6-triphosphorine (TAP) derivatives for the efficient formation of amide bonds via the dehydrative coupling of aromatic carboxylic acids with amines. The nontoxic and metal-free precatalyst TAP(catecholate)$_3$ (TAP-**1**) was used to provide a catalyst system based on catechol cyclic phosphate (CCP) and pyrocatechol phosphate (PP). The overall reaction seems to involve distinct stoichiometric and catalytic steps, and the interconversion between CCP and PP is likely the key to the catalytic process. Since phosphorus atoms are abundant in biological organisms and stored as adenosine triphosphate (ATP) for the activation of α-amino acids,[20] the developed method could potentially represent a promising method for the synthesis of di- and oligopeptides; such applications are currently under investigation in our laboratory.

All the commercial reagents and solvents were used as purchased. ^{1}H NMR spectra were recorded on a JEOL ECA-500 or ECA-600 (500 or 600 MHz) at r.t. Chemical shifts are presented in ppm δ relative to TMS, coupling constants in Hz, and integrations are based on the internal standard (1,1,2,2- tetrachloroethane). ^{13}C NMR spectra were recorded on Jeol ECA-500 or ECA-600 (125 or 150 MHz) at r.t. in $CDCl_3$ or DMSO-d_6. Chemical shifts were recorded in ppm based on the NMR solvent ($CDCl_3$ at 77.06 ppm). High-resolution spectra (HRMS) were obtained from JEOL JMS-700 (FAB) or Bruker compact-TOF. TLC analysis was performed on commercial glass plates bearing 0.25 mm layer of Merck TLC silica gel 60 GF254. Optical rotation value was recorded on Polarimeter P-1010-GT (JASCO). HPLC analysis was conducted on Shimadzu HPLC system. All reactions were performed in oven-dried glassware. TAPs **1**,[21] **3**,[22] and **7–9**[23] as well as amides **3aa–aj**[12] are known compounds.

TAP Derivatives; General Procedure

An oven-dried 100 mL two-necked round-bottom flask was equipped with a Teflon coated magnetic stirring bar. To seal the apparatus, a balloon was connected to the flask using a three-way stopcock; then, the atmosphere was replaced by N_2 gas. 1,3,5-Triazo-2,4,6-triphosphorine-2,2,4,4,6,6-hexachloride (TAP-**10**), the related catechol derivative, and the base were placed in the reaction mixture, following anhydrous solvent under N_2 flow. The reaction was allowed to stir. Upon completion, the product was purified by filtration or gradient column chromatography.

Tris(*o*-phenylenedioxy)cyclotriphosphazene (TAP-1)

According to the general procedure, the reaction was carried out between TAP-**10** (2.008 g, 6 mmol, 1.0 equiv), catechol (1.98 g, 18 mmol, 3.0 equiv), and K_2CO_3 (18 mmol, 3.0 equiv) in THF (60 mL) at r.t. for 48 h. TAP-**1** was obtained as a white solid after filtration and washing with THF (100 mL), and then H_2O (200 mL); yield: 1350 mg [2.94 mmol, 49 ± 5% (avg. of 8 runs)].

^{1}H NMR (DMSO-d_6, 600 MHz): δ = 7.29 (6 H, m), 7.09 (6 H, m).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 144.46, 123.82, 112.53.

^{31}P{H} NMR ($CDCl_3$): δ = 33.76.

Tris(4-methyl-*o*-phenylenedioxy)cyclotriphosphazene (TAP-2)

According to the general procedure, the reaction was carried out between TAP-**10** (696 mg, 2 mmol, 1.0 equiv), 4-methylcatechol (744 mg, 6 mmol, 3.0 equiv), and K_2CO_3 (6 mmol, 3.0 equiv) in THF (20 mL) at r.t. for 72 h. TAP-**2** was obtained as a white solid after column chromatography (EtOAc/*n*-hexane 1/5); yield: 130 mg (0.26 mmol, 13%); R_f = 0.52 (20% EtOAc in *n*-hexane).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 6.74–6.90 (9 H, m), 2.24 (9 H, s).

^{31}P{H} NMR ($CDCl_3$): δ = 34.24.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{18}N_3O_6P_3Na^+$: 524.0306; found: 524.0264.

Tris[4-(*tert*-butyl)-*o*-phenylenedioxy]cyclotriphosphazene (TAP-3)

According to the general procedure, the reaction was carried out between TAP-**10** (1.044 g, 3 mmol, 1.0 equiv), 4-*tert*-butylcatechol (1.494 g, 9 mmol, 3.0 equiv), and K_2CO_3 (9 mmol, 3.0 equiv) in THF (30 mL) at r.t. for 48 h. TAP-**3** was obtained as a magenta solid after column chromatography (EtOAc/*n*-hexane 1/5); yield: 282 mg (0.45 mmol, 15%); R_f = 0.75 (20% EtOAc in *n*-hexane).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 6.93–7.08 (9 H, m), 1.22 (27 H, s).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 147.60, 144.18, 142.05, 120.12, 111.53, 110.02, 34.91, 31.45.

^{31}P{H} NMR ($CDCl_3$): δ = 34.46.

HRMS (FAB): *m*/*z* [M + H]$^+$ calcd for $C_{30}H_{37}N_3O_6P_3^+$: 628.1895; found: 628.1876.

Tris(4-vinyl-*o*-phenylenedioxy)cyclotriphosphazene (TAP-4)

According to the general procedure, the reaction was carried out between TAP-**10** (905 mg, 2.6 mmol, 1.0 equiv), 4-vinylcatechol (1.06 g, 7.8 mmol, 3.0 equiv), and Na_2CO_3 (7.8 mmol, 3.0 equiv) in THF (30 mL) at r.t. for 72 h. TAP-**4** was obtained as a white solid after column chromatography (EtOAc/*n*-hexane 1/4); yield: 126 mg (0.23 mmol, 9%); R_f = 0.75 (25% EtOAc in *n*-hexane).

^{1}H NMR (DMSO-d_6, 600 MHz): δ = 7.13 (3 H), 6.99 (6 H), 6.56–6.60 (3 H, m), 5.58–5.61 (3 H, d, *J* = 17.4 Hz), 5.18–5.20 (3 H, d, *J* = 10.98 Hz).

^{31}P{H} NMR ($CDCl_3$): δ = 34.22.

TAP-**4** seems to be polymerized during an ESI-MS measurement.

Tris(4-chloro-*o*-phenylenedioxy)cyclotriphosphazene (TAP-5)

According to the general procedure, the reaction was carried out between TAP-**10** (696 mg, 2 mmol, 1.0 equiv), 4-chlorocatechol (867 mg, 6 mmol, 3.0 equiv), and Na_2CO_3 (6 mmol, 3.0 equiv) in THF (20 mL) at 66 °C for 72 h. TAP-**5** was obtained as a beige solid after column chromatography (DCM/MeOH 20/1); yield: 573 mg (1.02 mmol, 51%); R_f = 0.56 (5% MeOH in DCM).

^{1}H NMR (DMSO-d_6, 600 MHz): δ = 6.55–6.62 (9 H, m).

^{31}P{H} NMR ($CDCl_3$): δ = –79.28.

Due in part to structural instability of TAP-**5**, no relevant peaks were found by ESI-MS measurement.

Tris(4-nitro-*o*-phenylenedioxy)cyclotriphosphazene (TAP-6)

According to the general procedure, the reaction was carried out between TAP-**10** (174 mg, 0.5 mmol, 1.0 equiv), 4-nitrocatechol (233 mg, 1.5 mmol, 3.0 equiv), and Na_2CO_3 (3 mmol, 6.0 equiv) in THF (20 mL) at 66 °C for 72 h. TAP-**6** was obtained as a bright yellow solid after column chromatography (DCM/MeOH 20/1); yield: 211 mg (0.36 mmol, 71%); R_f = 0.14 (5% MeOH in DCM).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.71–7.72 (3 H, m), 7.53 (3 H, m), 6.88–6.90 (3 H, m).

^{31}P{H} NMR ($CDCl_3$): δ = –77.56.

Due in part to structural instability of TAP-**6**, no relevant peaks were found by ESI-MS measurement.

Hexakis(phenoxy)cyclotriphosphazene (TAP-7)

According to the general procedure, the reaction was carried out between TAP-**10** (1.044 g, 3 mmol, 1.0 equiv), phenol (1.778 g, 18.92 mmol, 6.3 equiv), and K_3PO_4 (34.46 mmol, 11.5 equiv) in MeCN (50 mL) at 88 °C (reflux) for 10 h, then the crude was allowed to cool to r.t. The solid was filtered and washed with EtOAc (2 × 50 mL), the filtrate and the washings were combined, and the solvent was removed under reduced pressure. TAP-**7** was obtained as white solid after column chromatography (DCM); yield: 1664.57 mg (2.4 mmol, 80%); R_f = 0.94 (DCM).

^{1}H NMR (DMSO-d_6, 600 MHz): δ = 7.14–7.18 (12 H, m), 7.08–7.12 (6 H, m), 6.91–6.92 (12 H, m).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 150.67, 129.46, 124.90, 121.12.

^{31}P{H} NMR ($CDCl_3$): δ = 9.32.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{36}H_{31}N_3O_6P_3^+$: 694.1426; found: 694.1398.

Hexakis(4-methoxyphenoxy)cyclotriphosphazene (TAP-8)

According to the general procedure, the reaction was carried out between TAP-**10** (1.044 g, 3 mmol, 1.0 equiv), *p*-methoxyphenol (2.327 g, 18.92 mmol, 6.3 equiv), and K_3PO_4 (34.46 mmol, 11.5 equiv) in MeCN (50 mL) at 88 °C (reflux) for 6 h, then the crude was allowed to cool to r.t. The solid was filtered and washed with EtOAc (2 × 50 mL) , the filtrate and the washings were combined, and the solvent was removed under reduced pressure. TAP-**8** was obtained as a white solid after column chromatography (EtOAc/*n*-hexane 1/1); yield: 2505.5 mg (2.9 mmol, 96%); R_f = 0.66 (EtOAc/*n*-hexane 1/1).

^{1}H NMR (DMSO-d_6, 600 MHz): δ = 6.81–6.84 (12 H, m), 6.66–6.68 (12 H, m), 3.76 (18 H, s).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 156.54, 144.35, 121.91, 114.31, 55.54.

^{31}P{H} NMR ($CDCl_3$): δ = 10.59.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{42}H_{43}N_3O_{12}P_3^+$: 874.2060; found: 874.2053.

Hexakis(4-nitrophenoxy)cyclotriphosphazene (TAP-9)

According to the general procedure, the reaction was carried out between TAP-**10** (1.044 g, 3 mmol, 1.0 equiv), *p*-nitrophenol (2.63 g, 18.92 mmol, 6.3 equiv), and K_3PO_4 (34.46 mmol, 11.5 equiv) in MeCN (50 mL) at 88 °C (reflux) for 10 h, then the crude was allowed to cool to r.t. The crude product was washed with acetone then with H_2O. TAP-**9** was recrystallized from *o*-dichlorobenzene; yield: 1734.39 mg (1.8 mmol, 60%).

^{1}H NMR (DMSO-d_6, 600 MHz): δ = 8.16 (12 H, m), 7.30–7.32 (12 H, m).

^{13}C NMR (DMSO-d_6, 150 MHz): δ = 154.15, 145.34, 126.32, 122.02.

^{31}P{H} NMR ($CDCl_3$): δ = 7.86.

Tris(4-methyl-*o*-phenylenediamino)cyclotriphosphazene (TAP-11)

According to the general procedure, the reaction was carried out between TAP-**10** (1.74 g, 5 mmol, 1.0 equiv), 3,4-diaminotoluene (1.83 g, 15 mmol, 3.0 equiv), and Et_3N (30 mmol, 6.0 equiv) in THF (50 mL) at r.t. for 21 h. Upon completion, the precipitate was collected by filtration and then washed with toluene. The material was recrystallized from MeOH/H_2O to yield white crystals of TAP-**11**; yield: 4830 mg (3.25 mmol, 65%).

^{1}H NMR (DMSO-d_6, 600 MHz): δ = 7.37 (3 H, m), 6.38 (3 H, s), 2.05 (9 H, s).

^{13}C NMR (DMSO-d_6, 150 MHz): δ = 135.01, 132.31, 125.60, 117.57, 115.32, 114.71, 20.46.

^{31}P{H} NMR ($CDCl_3$): δ = 19.60.

Amides; General Procedure

An oven-dried 50 mL two-necked round-bottom flask was equipped with a Teflon coated magnetic stirrer bar and connected to an azeotropic condenser. To seal the apparatus, a balloon was connected to the azeotropic condenser by a three-way stopcock; then, the atmosphere was replaced by N_2 gas. Under a flow of N_2, the flask was charged with the CA (0.5 mmol, 1 equiv) and TAP-**1** (11.48 mg, 5 mol%). Then, the amine (0.5 mmol, 1 equiv) was added under N_2 flow, followed by the solvent (dehydrated toluene or chlorobenzene; 7 mL). The reaction mixture was stirred under azeotropic reflux at 128 °C (133 °C in the case of chlorobenzene) for 16 h. Thereafter, the reaction flask was cooled to r.t., and the solvent was evaporated under reduced pressure using a rotary evaporator. The purification was performed by a three-step acid/base extraction. To this end, a separatory funnel was charged with H_2O and a DCM solution of the crude product mixture; after extraction, the organic layers (3 × 25 mL of DCM) were collected and washed with sat. aq Na_2CO_3 (25 mL). The aqueous layer was subsequently extracted with DCM (3 × 25 mL), and the organic phases were combined. The combined organic phases were washed with aq HCl (1 M, 25 mL). The aqueous phase was extracted with DCM (3 × 25 mL). The combined organic layers were washed with brine solution, dried over Na2SO4, and filtered. Finally the solvent of the filtrate was removed under reduced pressure.

***N*-Benzylbenzamide (3aa)**

According to the general procedure **3aa** was obtained as a white solid after extraction; yield: 85.56 mg (0.40 mmol, 81%).

^{1}H NMR (DMSO-d_6, 600 MHz): δ = 7.78–7.79 (2 H), 7.47–7.50 (1 H, t, J = 7.8 Hz), 7.39–7.42 (2 H, t, J = 8.4 Hz), 7.33–7.34 (4 H, d, J = 4.8 Hz), 7.28–7.30 (1 H, m), 6.56 (1 H, br), 4.62–4.63 (2 H, d, J = 5.4 Hz).

^{13}C NMR (DMSO-d_6, 150 MHz): δ = 167.43, 138.27, 134.48, 131.63, 128.89, 128.69, 128.02, 127.72, 127.04, 44.23.

***N*-Benzyl-4-methylbenzamide (3ba)**

According to the general procedure **3ba** was obtained as a white solid after extraction; yield: 90.12 mg (0.40 mmol, 80%).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.68–7.69 (2 H, d, J = 8.4 Hz), 7.33–7.34 (4 H, m), 7.27–7.30 (1 H, m), 7.20–7.21 (2 H, m), 6.48 (1 H, br), 4.61–4.62 (2 H, d, J = 6 Hz), 2.38 (3 H, s).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 167.35, 142.00, 138.40, 131.58, 129.28, 128.81, 127.95, 127.61, 127.02, 44.11, 21.49.

***N*-Benzyl-2-methylbenzamide (3ca)**

According to the general procedure **3ca** was purified by column chromatography as a white solid (EtOAc/*n*-hexane 1/1); yield: 46.15 mg (0.20 mmol, 41%); R_f = 0.75 (50% EtOAc in *n*-hexane).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.13–7.35 (9 H, m), 6.92 (1 H, br), 4.58–4.59 (2 H, d, J = 5.4 Hz), 2.42 (3 H, s).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 169.93, 138.23, 136.29, 136.25, 131.12, 130.00, 128.85, 127.90, 127.68, 126.70, 125.79, 43.98, 19.91.

HRMS (ESI): m/z [M + Na]$^+$ calcd for $C_{15}H_{15}NONa^+$: 248.1051; found: 248.1052.

***N*-Benzyl-4-(*tert*-butyl)benzamide (3da)**

According to the general procedure **3da** was obtained as a white solid after extraction; yield: 100.26 mg (0.38 mmol, 75%).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.72–7.74 (2 H, m), 7.42–7.44 (2 H, m), 7.34–7.35 (4 H, m), 7.27–7.30 (1 H, m), 6.47 (1 H, br), 4.63–4.64 (2 H, d, J = 6.6 Hz), 1.32 (9 H, s).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 167.31, 155.10, 138.42, 131.55, 128.80, 127.91, 127.60, 126.86, 125.57, 44.08, 34.97, 31.20.

***N*-Benzyl-3,5-di-*tert*-butylbenzamide (3ea)**

According to the general procedure **3ea** was obtained as a white solid after extraction; yield: 116.44 mg (0.36 mmol, 72%).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.62 (2 H, d, J = 1.8 Hz), 7.56–7.57 (1 H, m), 7.33–7.38 (4 H, m), 7.28–7.30 (1 H, m), 6.50 (1 H, br), 4.65–4.66 (2 H, d, J = 6 Hz), 1.33 (18 H, s).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 168.50, 151.37, 138.59, 134.11, 128.82, 128.01, 127.59, 125.82, 121.21, 44.17, 35.07, 31.48.

***N*-Benzyl-4-methoxybenzamide (3fa)**

According to the general procedure **3fa** was obtained as a white solid after extraction; yield: 86.86 mg (0.36 mmol, 72%).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.74–7.76 (2 H, m), 7.33–7.34 (3 H, m), 7.27–7.29 (1 H, m), 6.88–6.90 (2 H, m), 6.49 (1 H, br), 4.60–4.61 (2 H, d, *J* = 5.4 Hz), 3.83 (3 H, s).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 166.98, 162.29, 138.54, 128.89, 128.82, 127.97, 127.60, 126.74, 113.84, 55.49, 44.12.

***N*-Benzyl-3,5-dimethoxybenzamide (3ga)**

According to the general procedure **3ga** was obtained as a white solid after extraction; yield: 97.67 mg (0.36 mmol, 72%).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.32–7.34 (4 H, m), 7.28–7.29 (1 H, m), 6.91–6.92 (2 H, d, *J* = 3 Hz), 6.54–6.56 (2 H, m), 4.59–4.61 (2 H, d, *J* = 6 Hz), 3.79 (6 H, s).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 167.29, 160.98, 138.22, 136.70, 128.85, 127.96, 127.67, 105.02, 103.70, 55.64, 44.23.

***N*-Benzyl-4-(methylthio)benzamide (3ha)**

According to the general procedure **3ha** was obtained as a white solid after extraction; yield: 120.95 mg (0.47 mmol, 94%).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.65–7.67 (2 H, m), 7.28–7.30 (4 H, m), 7.23–7.25 (1 H, m), 7.17–7.18 (2 H, m), 6.52 (1 H, br), 4.56–4.57 (2 H, d, *J* = 6 Hz), 2.44 (3 H, s).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 166.90, 143.54, 138.32, 130.52, 128.81, 127.94, 127.63, 127.45, 125.48, 44.13, 15.09.

***N*-Benzyl-4-(dimethylamino)benzamide (3ia)**

According to the general procedure [chlorobenzene (7 mL), 133 °C], **3ia** was obtained as a white solid after extraction; yield: 103.00 mg (0.40 mmol, 81%).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.69–7.71 (2 H, m), 7.31–7.34 (4 H, m), 7.25–7.28 (1 H, m), 6.63–6.66 (2 H, m), 6.37 (1 H, m), 4.61–4.62 (2 H, d, *J* = 5.4 Hz), 2.99 (6 H, s).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 167.34, 152.55, 138.94, 128.72, 128.53, 127.91, 127.41, 121.16, 111.13, 43.95, 40.16.

***N*-Benzyl-4-chlorobenzamide (3ja)**

According to the general procedure **3ja** was obtained as a white solid after extraction; yield: 105.65 mg (0.43 mmol, 86%).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.71–7.75 (2 H, m), 7.28–7.39 (7 H, m), 6.50 (1 H, br), 4.61–4.62 (2 H, d, *J* = 5.4 Hz).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 166.36, 138.00, 137.85, 132.78, 128.88, 128.47, 127.98, 127.77, 44.28.

***N*-Benzyl-4-iodobenzamide (3ka)**

According to the general procedure **3ka** was obtained as a white solid after extraction; yield: 133.18 mg (0.40 mmol, 79%).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.76–7.77 (2 H, m), 7.50–7.51 (2 H, m), 7.29–7.37 (5 H, m), 6.45 (1 H, br), 4.61–4.62 (2 H, d, *J* = 5.4 Hz).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 166.60, 137.96, 137.85, 133.82, 128.89, 128.62, 127.99, 127.80, 98.55, 44.28.

***N*-Benzyl-4-nitrobenzamide (3la)**

According to the general procedure [chlorobenzene (7 mL), 133 °C], **3la** was obtained as a white solid after extraction; yield: 125.57 mg (0.49 mmol, 98%).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.22–8.24 (2 H, m), 7.92–7.94 (2 H, m), 7.29–7.36 (5 H, m), 6.80 (1 H, br), 4.62–4.63 (2 H, d, *J* = 6 Hz).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 165.47, 149.64, 139.96, 137.53, 128.95, 128.27, 127.96, 123.84, 44.47.

***N*-Benzylfuran-2-carboxamide (3ma)**

According to the general procedure **3ma** was obtained as a white solid after extraction; yield: 82.50 mg (0.41 mmol, 82%).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.25–7.40 (6 H, m), 7.14 (1 H, d, *J* = 3 Hz), 6.69 (1 H, br), 6.49 (1 H, m), 4.60–4.61 (2 H, d, *J* = 5.4 Hz).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 158.45, 148.09, 144.05, 138.20, 128.95, 128.09, 127.81, 114.55, 112.34, 43.34.

***N*-Benzylthiophene-2-carboxamide (3na)**

According to the general procedure **3na** was obtained as a white solid after extraction; yield: 72.79 mg (0.34 mmol, 67%).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.51–7.52 (1 H, dd, *J* = 4.2, 1.8 Hz), 7.46–7.47 (1 H, dd, *J* = 4.8, 1.2 Hz), 7.32–7.34 (4 H, m), 7.27–7.30 (1 H, m), 7.04–7.06 (1 H, m), 6.45 (1 H, br), 4.59–4.60 (2 H, d, *J* = 6 Hz).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 161.92, 138.86, 138.15, 130.11, 128.86, 128.25, 128.01, 127.72, 44.07.

***N*-Benzylbenzofuran-2-carboxamide (3oa)**

According to the general procedure **3oa** was obtained as a white solid after extraction; yield: 114.33 mg (0.46 mmol, 91%).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.64–7.66 (1 H, d, *J* = 8.4 Hz), 7.49 (1 H, s), 7.44–7.45 (1 H, m), 7.34–7.40 (5 H, m), 7.24–7.31 (2 H, m), 7.01 (1 H, br), 4.66–4.67 (2 H, d, *J* = 6.6 Hz).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 158.86, 154.79, 148.67, 137.85, 128.88, 128.05, 127.79, 127.66, 126.95, 123.77, 112.81, 111.78, 110.70, 43.46.

***N*-Benzylpicolinamide (3pa)**

According to the general procedure **3pa** was obtained as a white solid after extraction; yield: 90.21 mg (0.42 mmol, 85%).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.52 (1 H, d, *J* = 4.2 Hz), 8.38 (1 H, br), 8.23–8.24 (1 H, d, *J* = 7.2 Hz), 7.83–7.86 (1 H, m), 7.40–7.42 (1 H, m), 7.33–7.38 (4 H, m), 7.26–7.29 (1 H, m), 4.67–4.68 (2 H, d, *J* = 6 Hz).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 164.29, 149.91, 148.13, 138.28, 137.41, 128.76, 127.90, 127.52, 126.25, 122.40, 43.55.

***N*-hexylbenzamide (3ab)**

According to the general procedure **3ab** was obtained as a white solid after extraction; yield: 83.15 mg (0.40 mmol, 81%).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.75–7.77 (2 H, d, *J* = 6.6 Hz), 7.46–7.49 (1 H, m), 7.40–7.43 (2 H, m), 6.27 (1 H, br), 3.42–3.45 (2 H, m), 1.58–1.63 (2 H, m), 1.29–1.40 (6 H, overlapping), 0.88–0.90 (3 H, t, *J* = 6.6 Hz).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 167.61, 134.98, 131.33, 128.58, 126.93, 40.20, 31.59, 29.72, 26.75, 22.64, 14.09.

N-Cyclohexylbenzamide (3ac)

According to the general procedure **3ac** was obtained as a white solid after extraction; yield: 67.08 mg (0.33 mmol, 66%).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.74–7.76 (2 H, d, *J* = 7.2 Hz), 7.40–7.49 (3 H, m), 6.01 (1 H, br), 3.95–4.00 (1 H, m), 2.02–2.04 (2 H, m), 1.74–1.77 (2 H, dt, *J* = 7.8, 3.6 Hz), 1.63–1.67 (1 H, dt, *J* = 7.8, 3.6 Hz), 1.39–1.46 (2 H, m), 1.19–1.27 (3 H, m).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 166.70, 135.21, 131.30, 128.58, 126.90, 48.75, 33.32, 25.66, 25.00.

(2-Methylpiperidin-1-yl)(phenyl)methanone (3ad)

According to the general procedure **3ad** was purified by column chromatography as a white solid (EtOAc/*n*-hexane 1/1); yield: 7.11 mg (0.04 mmol, 7%); R_f = 0.55 (50% EtOAc in *n*-hexane).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.35–7.39 (5 H, m), 3.59–5.07 (2 H, br), 2.96 (1 H, br), 1.41–1.64 (6 H, m), 1.21 (3 H, s).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 170.53, 137.18, 129.19, 128.50, 126.44, 30.38 (br), 26.14 (br), 18.97, 16.27 (br) (3 C overlapped in broad peaks).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{17}NONa^+$: 226.1208; found: 226.1201.

Phenyl(pyrrolidin-1-yl)methanone (3ae)

According to the general procedure **3ae** was obtained as a white solid after extraction; yield: 70.09 mg (0.40 mmol, 80%).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.50–7.52 (2 H, m), 7.37–7.41 (3 H, m), 3.64–3.66 (2 H, t, *J* = 6.6 Hz), 3.41–3.44 (2 H, t, *J* = 7.2 Hz), 1.94–1.98 (2 H, m), 1.85–1.89 (2 H, m).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 169.80, 137.35, 129.82, 128.31, 127.15, 49.67, 46.23, 26.48, 24.54.

***N*,*N*-Dipropylbenzamide (3af)**

According to the general procedure **3af** was purified by column chromatography as a white solid (EtOAc/*n*-hexane 1/1); yield: 8.21 mg (0.04 mmol, 8%); R_f = 0.71 (50% EtOAc in *n*-hexane).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.29–7.32 (5 H, m), 3.49 (2 H), 3.10 (2 H), 1.63 (2 H), 1.46 (2 H), 0.92 (3 H), 0.68 (3 H).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 171.82, 137.46, 129.03, 128.38, 126.49, 50.72, 46.31, 21.95, 20.75, 11.46, 11.05.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{19}NONa^+$: 228.1364; found: 228.1357.

Morpholino(phenyl)methanone (3ag)

According to the general procedure **3ag** was obtained as a white solid after extraction; yield: 60.24 mg (0.32 mmol, 63%).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.39–7.43 (5 H, m), 3.45–3.78 (8 H, overlapping).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 170.51, 135.42, 129.95, 128.64, 127.16, 66.98, 48.32, 43.17.

***N*-(Furan-2-ylmethyl)benzamide (3ah)**

According to the general procedure **3ah** was obtained as a white solid after extraction; yield: 70.43 mg (0.35 mmol, 70%).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.78–7.79 (2 H, d, *J* = 7.2 Hz), 7.48–7.51 (1 H, m), 7.41–7.43 (2 H, m), 7.37 (1 H), 6.51 (1 H, br), 6.33–6.34 (1 H, dd, *J* = 3, 1.8 Hz), 6.29 (1 H, d, *J* = 2.4 Hz), 4.63–4.64 (2 H, d, *J* = 6 Hz).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 167.29, 151.26, 142.40, 134.26, 131.69, 128.66, 127.08, 110.61, 107.78, 37.09.

***N*-Phenylbenzamide (3ai)**

According to the general procedure **3ai** was obtained as a white solid after extraction; yield: 13.81 mg (0.07 mmol, 14%).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 7.86–7.88 (2 H, m), 7.81 (1 H, br), 7.64–7.65 (2 H, d, *J* = 7.2 Hz), 7.54–7.56 (1 H, m), 7.48–7.51 (2H, t, *J* = 7.8 Hz), 7.37–7.39 (2H, m), 7.14–7.17 (1H, m).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 165.78, 137.99, 135.11, 131.95, 129.20, 128.91, 127.08, 124.67, 120.24.

(*S*)-*N*-[1-(1*H*-indol-3-yl)-3-methoxybut-3-en-2-yl]benzamide (3aj)

According to the general procedure **3aj** was purified by column chromatography as a white solid (EtOAc/*n*-hexane 1/1); yield: 57.77 mg (0.16 mmol, 32%); R_f = 0.57 (50% EtOAc in *n*-hexane); $[\alpha]_D^{20}$ +74.7 (*c* 0.40, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 600 MHz): δ = 8.08 (1 H, s), 7.67–7.69 (2 H, m), 7.54–7.55 (1 H, d, *J* = 7.92 Hz), 7.46–7.47 (1 H, m), 7.35–7.39 (3 H, m), 7.17–7.20 (1 H, m), 7.07–7.09 (1 H, m), 7.01 (1 H, d, *J* = 2.4 Hz), 6.65–6.66 (1 H, d, *J* = 7.5 Hz), 5.14–5.16 (1 H, m), 3.72 (3 H, s), 3.42–3.46 (2 H, m).

^{13}C NMR ($CDCl_3$, 150 MHz): δ = 172.58, 166.90, 136.13, 133.94, 131.77, 128.61, 127.86, 127.16, 122.86, 122.41, 119.86, 118.80, 111.35, 110.23, 53.53, 52.52, 27.76.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{18}N_2O_3Na^+$: 345.1215; found: 345.1213.

Funding Information

This work was supported by a MEXT Grant-in-aid for Scientific Research on Innovative Areas (18H04247 to SS) and a JSPS Scientific Research (B) (19H02713 to SS); and partially funded by Japan Society for the Promotion of Science (JSPS) fellowship for foreign researchers (P18339 to DB).

Acknowledgment

We acknowledge Messrs K. Oyama, Y. Maeda, H. Okamoto, and Ms. H. Natsume for technical support.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707174.

References

(1) Vinogradov, A. A.; Yin, Y.; Suga, H. *J. Am. Chem. Soc.* **2019**, *141*, 4167.
(2) Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. *J. Comb. Chem.* **1999**, *1*, 55.
(3) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411.
(4) Jursic, B. S.; Zdravkovdki, Z. *Synth. Commun.* **1993**, *23*, 2761.

(5) (a) Carpino, L. A. *J. Am. Chem. Soc.* **1993**, *115*, 4397. (b) El-Faham, A.; Albericio, F. *J. Pept. Sci.* **2010**, *16*, 6. (c) Subiros-Funosas, R.; Prohens, R.; Barbas, R.; El-Faham, A.; Albericio, F. *Chem. Eur. J.* **2009**, *15*, 9394. (d) König, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788. (e) König, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 2034.

(6) (a) de Azambuja, F.; Parac-Vogt, T. N. *ACS Catal.* **2019**, *9*, 10245. (b) Lundberg, H.; Tinnis, F.; Selander, N.; Adolfsson, H. *Chem. Soc. Rev.* **2014**, *43*, 2714. (c) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471. (d) de Figueiredo, R. M.; Suppo, J. S.; Campagne, J. M. *Chem. Rev.* **2016**, *116*, 12029. (e) Georgiou, I.; Ilyashenko, G.; Whiting, A. *Acc. Chem. Res.* **2009**, *42*, 756. (f) Charville, H.; Jackson, D.; Hodges, G.; Whiting, A. *Chem. Commun.* **2010**, *46*, 1813.

(7) (a) Muramatsu, W.; Hattori, T.; Yamamoto, H. *J. Am. Chem. Soc.* **2019**, *141*, 12288. (b) Muramatsu, W.; Yamamoto, H. *J. Am. Chem. Soc.* **2019**, *141*, 18926. (c) Tsuji, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2016**, *138*, 14218.

(8) Handoko; Satishkumar, S.; Panigrahi, N. R.; Arora, P. S. *J. Am. Chem. Soc.* **2019**, *141*, 15977.

(9) (a) Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4196. (b) Ishihara, K.; Kondo, S.; Yamamoto, H. *Synlett* **2001**, 1371. (c) Ishihara, K.; Ohara, S.; Yamamoto, H. *Macromolecules* **2000**, *33*, 3511. (d) Maki, T.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2006**, *8*, 1431. (e) Maki, T.; Ishihara, K.; Yamamoto, H. *Tetrahedron* **2007**, *63*, 8645. (f) Al-Zoubi, R. M.; Marion, O.; Hall, D. G. *Angew. Chem. Int. Ed.* **2008**, *47*, 2876. (g) Sakakura, A.; Ohkubo, T.; Yamashita, R.; Akakura, M.; Ishihara, K. *Org. Lett.* **2011**, *13*, 892. (h) Sakakura, A.; Yamashita, R.; Ohkubo, T.; Akakura, M.; Ishihara, K. *Aust. J. Chem.* **2011**, *64*, 1458. (i) Gernigon, N.; Al-Zoubi, R. M.; Hall, D. G. *J. Org. Chem.* **2012**, *77*, 8386. (j) Yamashita, R.; Sakakura, A.; Ishihara, K. *Org. Lett.* **2013**, *15*, 3654. (k) Ishihara, K. *Top. Organomet. Chem.* **2015**, *49*, 243. (l) Mohy El Dine, T.; Erb, W.; Berhault, Y.; Rouden, J.; Blanchet, J. *J. Org. Chem.* **2015**, *80*, 4532. (m) Ishihara, K.; Lu, Y. *Chem. Sci.* **2016**, *7*, 1276. (n) Lu, Y.; Wang, K.; Ishihara, K. *Asian J. Chem.* **2017**, *6*, 1191. (o) Wang, K.; Lu, Y.; Ishihara, K. *Chem. Commun.* **2018**, *54*, 5410. (p) Arkhipenko, S.; Sabatini, M. T.; Batsanov, A. S.; Karaluka, V.; Sheppard, T. D.; Rzepa, H. S.; Whiting, A. *Chem. Sci.* **2018**, *9*, 1058.

(10) (a) Noda, H.; Furutachi, M.; Asada, Y.; Shibasaki, M.; Kumagai, N. *Nat. Chem.* **2017**, *9*, 571. (b) Liu, Z.; Noda, H.; Shibasaki, M.; Kumagai, N. *Org. Lett.* **2018**, *20*, 612. (c) Opie, C. R.; Noda, H.; Shibasaki, M.; Kumagai, N. *Chem. Eur. J.* **2019**, *25*, 4648. (d) Noda, H.; Asada, Y.; Shibasaki, M.; Kumagai, N. *J. Am. Chem. Soc.* **2019**, *141*, 1546.

(11) (a) Charville, H.; Jackson, D. A.; Hodges, G.; Whiting, A.; Wilson, M. R. *Eur. J. Org. Chem.* **2011**, 5981. (b) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827. (c) Perreux, L.; Lpoupy, A.; Volatron, F. *Tetrahedron* **2002**, *58*, 2155.

(12) Sawant, D. N.; Bagal, D. B.; Ogawa, S.; Selvam, K.; Saito, S. *Org. Lett.* **2018**, *20*, 4397.

(13) (a) de Oliveira, V. M.; de Jesus, R. S.; Gomes, A. F.; Gozzo, F. C.; Umpierre, A. P.; Suarez, P. A. Z.; Rubim, J. C.; Neto, B. A. D. *ChemCatChem* **2011**, *3*, 1911. (b) Allen, C. L.; Chhatwal, A. R.; Williams, J. M. J. *Chem. Commun.* **2012**, *48*, 666. (c) Rahman, M.; Kundu, D.; Hajra, A.; Majee, A. *Tetrahedron Lett.* **2010**, *51*, 2896. (d) Shekhar, A. C.; Kumar, A. R.; Sathaiah, G.; Paul, V. L.; Sridhar, M.; Rao, P. S. *Tetrahedron Lett.* **2009**, *50*, 7099. (e) Reddy, C. S.; Nagaraj, A.; Jalapathi, P. *Chin. Chem. Lett.* **2007**, *18*, 1213. (f) Allen, C. L.; Williams, J. M. J. *Chem. Soc. Rev.* **2011**, *40*, 3405.

(14) (a) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203. (b) Kokare, N. D.; Nagawade, R. R.; Rane, V. P.; Shinde, D. B. *Synthesis* **2007**, 766. (c) Klose, J.; Bienert, M.; Mollenkopf, C.; Wehle, D.; Zhang, C. W.; Carpino, L. A.; Henklein, P. *Chem. Commun.* **1999**, 1847. (d) Brady, S. F.; Freidinger, R. M.; Paleveda, W. J.; Colton, C. D.; Homnick, C. F.; Whitter, W. L.; Curley, P.; Nutt, R. F.; Veber, D. F. *J. Org. Chem.* **1987**, *52*, 764. (e) Ying, J.; Lin, R.; Xu, P.; Wu, Y.; Liu, Y.; Zhao, Y. *Sci. Rep.* **2018**, *8*, 936.

(15) Bayne, J. M.; Stephan, D. W. *Chem. Soc. Rev.* **2016**, *45*, 765.

(16) (a) Sakakura, A.; Sakuma, M.; Katsukawa, M.; Ishihara, K. *Heterocycles* **2008**, *76*, 657. (b) Yadav, M.; Krishnamurthy, R. *Org. Lett.* **2019**, *21*, 7400.

(17) (a) Du, Y.; Oishi, S.; Saito, S. *Chem. Eur. J.* **2011**, *17*, 12262. (b) Foo, S. W.; Oishi, S.; Saito, S. *Tetrahedron Lett.* **2012**, *53*, 5445.

(18) (a) Allcock, H. R.; Walsh, E. J. *J. Am. Chem. Soc.* **1972**, *94*, 4538. (b) Allcock, H. R.; Walsh, E. J. *J. Am. Chem. Soc.* **1969**, *91*, 3102. (c) Allcock, H. R. *Chem. Rev.* **1972**, *72*, 315. (d) Allcock, H. R.; Walsh, E. J. *J. Am. Chem. Soc.* **1972**, *94*, 119.

(19) Allcock, H. R.; Sunderland, N. J. *Macromolecules* **2001**, *34*, 3069.

(20) (a) Knowles, J. R. *Annu. Rev. Biochem.* **1980**, *49*, 877. (b) Wiegand, T. W.; Janssen, R. C.; Eaton, B. E. *Chem. Biol.* **1997**, *4*, 675. (c) Wilcox, M.; Nirenberg, M. *Proc. Natl. Acad. Sci. U. S. A.* **1968**, *61*, 229.

(21) (a) Tian, N.-N.; Wang, L.-S.; Jiang, R.-Y. *J. Chem. Eng. Data* **2011**, *56*, 3208. (b) Zhou, F.; Gu, K. H.; Zhang, Z. Y.; Zhang, M. Y.; Zhou, S.; Shen, Z.; Fan, X. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 15007. (c) Comotti, A.; Bracco, S.; Ferretti, L.; Mauri, M.; Simonutti, R.; Sozzani, P. *Chem. Commun.* **2007**, 350.

(22) Saito, S.; Noyori, R. JP Patent filed: 2013-065083; opened: 2014-189509, **2014**.

(23) Ye, C.; Zhang, Z.; Liu, W. *Synth. Commun.* **2002**, *32*, 203.