Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/d0ob01271h

Received 21st June 2020,
Accepted 9th July 2020

DOI: 10.1039/d0ob01271h

rsc.li/obc

Nickel/briphos-catalyzed transamidation of unactivated tertiary amides†

Dahyeon Yang,[a] Taeil Shin,[b] Hyunwoo Kim *[b] and Sunwoo Lee *[a]

The transamidation of tertiary amides was achieved *via* nickel catalysis in combination with briphos ligands. *N*-Methyl-*N*-phenylbenzamide derivatives reacted with primary amines in the presence of $NiCl_2$/briphos L4 to provide the transamidated products in moderate to good yields. Primary aromatic amines delivered higher product yields than aliphatic amines.

The amide functionality is a fundamental motif of peptide bonds present in life-essential proteins such as enzymes.[1] It is ubiquitous in bioactive molecules such as natural products, pharmaceuticals, and agrochemicals.[2] Due to the essentiality of amides, a number of synthesis methods have been developed for their efficient preparation.[3] Frequently employed amide synthesis methods include the reaction of amines with activated carboxylic acid derivatives,[4] oxidative amidation,[5] hydration of nitriles[6], and aminocarbonylation.[7] Recently, transamidation has garnered increasing attention, as a variety of amide products can be directly prepared *via* the reaction of amines with amide substrates.[8]

In the early development stages, transamidations were predominantly performed with primary amides, due to their high reactivity.[9] The transamidation of secondary amides with primary amines results in a mixture of two different amides, that is, the starting material and the product.[10] The introduction of activating groups and the employment of transition metal catalysts have largely resolved this drawback. A number of activating groups, such as *N*-tosyl, *N*-Boc, *N*-acetyl, and *N*-triflyl groups, have been employed for the activation of the amide C–N bond, promoting improved yields of the desired products.[11] Particularly, activated tertiary amides, such as glutarimide and saccharine, exhibit good activity in C–N bond cleavage for reaction with nucleophiles under transition metal catalyst and metal-free conditions.[12]

The transamidation of unactivated tertiary amides, such as *N*-methyl-*N*-phenylbenzamide, has likewise been developed by several groups. An earlier approach by the Stahl group entailed the reaction of a tertiary amide with a secondary amine in the presence of a Lewis acid catalyst to provide equilibrium mixtures.[13] In 2018, the Hu group developed a manganese-mediated reductive transamidation of tertiary amides with nitroarenes.[14] In addition, the Szostak group demonstrated the transformation of a tertiary amide to a different amide in the presence of LiHMDS.[15]

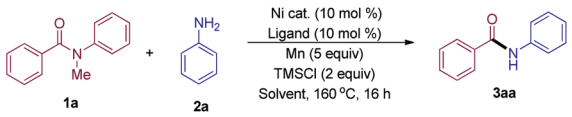
Recently, we reported the successful nickel-catalyzed C–N bond activation of amides for reaction with amines or the α-carbon of amides.[16] It was established that the combination of Ni(diglym)Cl_2 and a briphos ligand displayed favorable activity for the transamidation of unactivated secondary amides to provide the desired transamidated products in good yields. Briphos is a tunable π-acceptor phosphorus ligand effectively utilized for low-valent transition metal catalysis.[17] During our studies on transamidation, we established that unactivated tertiary amides also underwent transamidation to secondary amides in the presence of nickel/briphos. Herein, we report the Ni/briphos-catalyzed transamidation of tertiary amides.

N-Methyl-*N*-phenylbenzamide and aniline were allowed to react under various conditions (Table 1). Nickel(II) species were employed in the presence of manganese, as nickel(II) is air-stable. In addition, all reactions were conducted using trimethylsilyl chloride as an activator in the nickel catalyzed transamidation, as introduced in our previous report.[16a] First, numerous nickel sources were tested with non-substituted phenyl-based briphos **L1**. All the nickel(II) catalysts tested provided the transamidated product **3aa** in moderate yield (entries 1–7). Among them, the best results were obtained with $NiCl_2$ (entry 7). Thereafter, using $NiCl_2$ as the catalyst, various substituted briphos ligands, as shown in Fig. 1, were tested. *N*-3,5-Dimethylphenyl substituted briphos **L2** afforded **3aa** in

[a]Department of Chemistry, Chonnam National University, Gwangju 61186, Republic of Korea. E-mail: sunwoo@chonnam.ac.kr
[b]Department of Chemistry, KAIST, Daejeon 34141, Republic of Korea. E-mail: hwkim@kaist.edu

†Electronic supplementary information (ESI) available. See DOI: 10.1039/d0ob01271h

Table 1 Optimization of conditions for transamidation using briphos ligands[a]



Entry	Ni	Ligand[b]	Solvent	Yield[c] (%)
1	$Ni(OH)_2$	**L1**	NMP	50
2	$Ni(OAc)_2$	**L1**	NMP	45
3	$Ni(OTf)_2$	**L1**	NMP	50
4	NiF_2	**L1**	NMP	45
5	$Ni(PPh_3)_2Cl_2$	**L1**	NMP	40
6	$Ni(glyme)Cl_2$	**L1**	NMP	42
7	$NiCl_2$	**L1**	NMP	66
8	$NiCl_2$	**L2**	NMP	69
9	$NiCl_2$	**L3**	NMP	70
10	$NiCl_2$	**L4**	NMP	87
11	$NiCl_2$	**L5**	NMP	65
12	$NiCl_2$	**L6**	NMP	69
13	$NiCl_2$	**L4**	DMAc	62
14	$NiCl_2$	**L4**	DMSO	20
15	$NiCl_2$	**L4**	Diglyme	55
16[d]	$NiCl_2$	**L4**	NMP	77
17[e]	$NiCl_2$	**L4**	NMP	64
18[f]	$NiCl_2$	**L4**	NMP	22

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), Ni (0.02 mmol), ligand (0.02 mmol), TMSCl (0.4 mmol), and Mn (1.0 mmol) were reacted at 160 °C for 16 h. [b] Briphos ligands. [c] Isolated yield. [d] Mn (0.6 mmol) was used. [e] Reaction time was 6 h. [f] Reaction temperature was 120 °C.

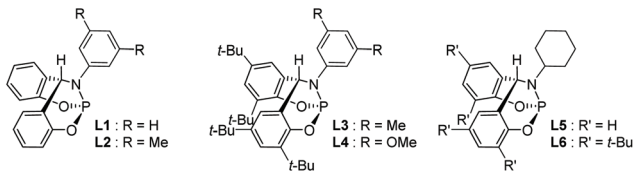
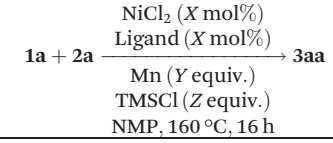


Fig. 1 Structures of briphos ligands.

69% yield (entry 8). Subsequently, 2,4-di-*tert*-butyl substituted phenyl-based briphos ligands (*t*-Bu-briphos) were evaluated. Methyl-, *tert*-butyl and methoxy substituted *t*-Bu-briphos **L3** and **L4** provided **3aa** in 70% and 87% yields, respectively (entries 9 and 10). *N*-Cyclohexyl-substituted briphos **L5** and **L6** provided **3aa** in 65% and 69% yields, respectively (entries 11 and 12). With **L4** being the ligand of choice, various solvents such as DMAc, DMSO, and diglyme were evaluated. However, all the solvents afforded inferior yields compared to NMP (entries 13–15). Decreasing the amount of Mn to three molar equivalents, shortening the reaction time to 6 h, and lowering the reaction temperature to 120 °C resulted in decreased product yields of 77%, 64%, and 22%, respectively (entries 16–18). Based on these results, the optimized conditions are as follows: amide (1.0 equiv.), amine (2.0 equiv.), $NiCl_2$ (10 mol%), **L4** (10 mol%), Mn (5.0 equiv.), and TMSCl (2.0 equiv.), reacted in NMP at 160 °C for 16 h.

Table 2 Transamidation of **1a** and **2a** under various conditions[a]

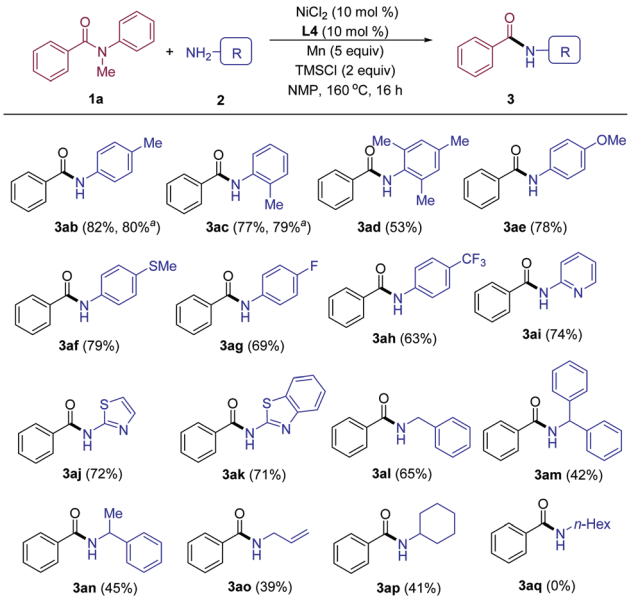


Entry	*X*	Ligand	*Y*	*Z*	Yield[b] (%)
1	10	PPh_3	5	2	45
2	10	PCy_3	5	2	38
3	5	**L4**	5	2	74(5)[c]
4	1	**L4**	5	2	31(15)[c]
5	0	—	5	2	Trace(20)[c]
6	10	**L4**	2	2	52
7	10	**L4**	1	2	42
8	10	**L4**	0	2	Trace
9	10	**L4**	5	4	87
10	10	**L4**	5	2[d]	84

[a] Reaction conditions: **1a** (0.2 mmol) and **2a** (0.4 mmol) were reacted in NMP at 160 °C for 16 h. [b] Isolated yield. [c] The yield of 3-benzoyl-1-methylpyrrolidin-2-one. [d] TMSI was used instead of TMSCl.

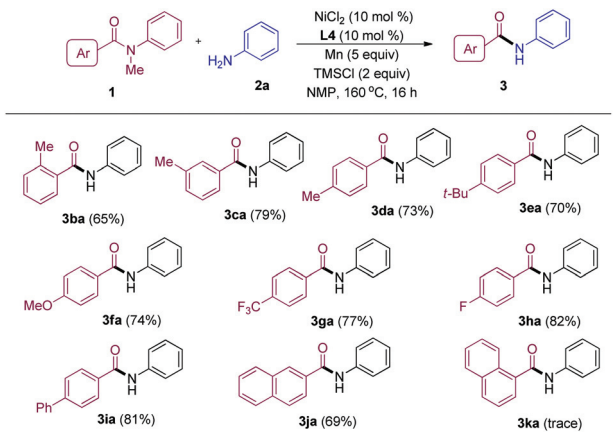
To study the optimal conditions in detail, the standard reactions were conducted under various different conditions (Table 2). The employment of PPh_3 and PCy_3 afforded **3aa** in 45% and 38% yields, respectively (entries 1 and 2). When the Ni quantity was reduced to 5 and 1 mol%, **3aa** was formed in 74% and 31% yields, respectively (entries 3 and 4). The reaction without a Ni catalyst provided a trace amount of **3aa** (entry 5). It was found that an unexpected by-product, which was generated from the reaction of **1a** and NMP, was formed when the amount of Ni employed was less than 10 mol%. Decreasing the amount of Mn to 2 and 1 equivalents provided **3aa** in 52% and 42% yields, respectively (entries 6 and 7). When the reaction was carried out without Mn, a trace amount of **3aa** was observed (entry 8). These results imply that a large amount of Mn was required to obtain **3aa** in high yield. Increasing the amount of TMSCl to 4 equivalents resulted in **3aa** in 87% yield (entry 9). The reaction with TMSI instead of TMSCl provided **3aa** in 84% yield (entry 10).

With the optimized conditions in hand, the substrate scope was investigated (Scheme 1). A variety of primary amines were allowed to react with **1a** under the optimized conditions. *Para*- and *ortho*-toluidines afforded the corresponding transamidated products **3ab** and **3ac** in 82% and 77% yields, respectively. The reaction with 2,4,6-trimethylaniline provided **3ad** in a slightly reduced yield, due to the steric hindrance of 2,4,6-trimethylaniline. 4-Methoxy- and 4-methylthio-anilines afforded **3ae** and **3af**, respectively, in good yields. 4-Fluoro- and 4-trifluoromethyl anilines gave **3ag** and **3ah** in 69% and 63% yields, respectively. Primary amines bearing heteroaromatic rings, such as pyridine, thiazol, and benzothiazole rings, likewise provided the corresponding amides **3ai**, **3aj**, and **3ak**, respectively, in good yields. Alkyl substituted primary amines, such as allyl amine and cyclohexyl amine, produced the corresponding amides **3ao** and **3ap** in 39% and 41% yields, respectively. However, *n*-hexyl amine did not generate the desired product **3aq**.

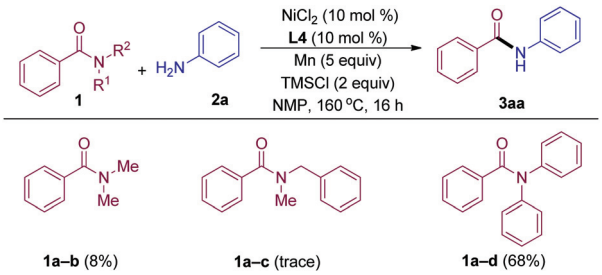


Scheme 1 Transamidation of **1a** with various primary amines. Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $NiCl_2$ (0.02 mmol), **L4** (0.02 mmol), TMSCl (0.4 mmol), and Mn (1.0 mmol) were reacted in NMP (1.0 mL) at 160 °C for 16 h. [a]**1a** (1.5 mmol) was used.

Subsequently, various substituted aryl amide derivatives were allowed to react with aniline under the optimized conditions (Scheme 2). 2-, 3-, and 4-Methyl substituted *N*-methyl-*N*-phenylbenzamides **1b**, **1c** and **1d** exhibited good yields in the formation of **3ba**, **3ca**, and **3da**, respectively. *N*-Methyl-*N*-phenylbenzamide derivatives, bearing *tert*-butyl, methoxy, trifluoromethyl, fluoride, and phenyl groups at the *para*-position of benzamide, provided the corresponding amides **3ea**, **3fa**, **3ga**, **3ha**, and **3ia** in good yields. *N*-Methyl-*N*-phenyl-2-naphthamide afforded **3ja** in 69% yield. However, only a trace amount of **3ka** was formed from *N*-methyl-*N*-phenyl-1-naphthamide.



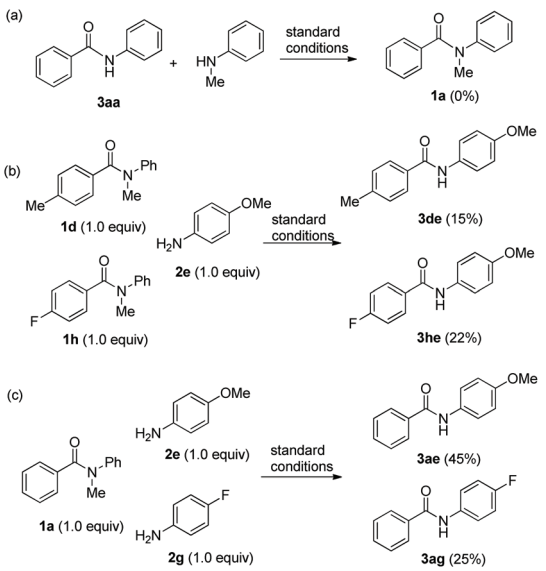
Scheme 2 Transamidation with substituted *N*-methyl-*N*-phenylbenzamide derivatives with aniline. Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $NiCl_2$ (0.02 mmol), **L4** (0.02 mmol), TMSCl (0.4 mmol), and Mn (1.0 mmol) were reacted in NMP (1.0 mL) at 160 °C for 16 h.



Scheme 3 Reactions of benzamide derivatives with aniline.

Unactivated tertiary benzamides **1a–b**, **1a–c**, and **1a–d** were evaluated in the reaction with aniline under standard conditions, as shown in Scheme 3. *N*,*N*-dimethyl- and *N*-methyl-*N*-benzyl benzamides provided considerably low yields of **3aa**. *N*,*N*-Diphenylbenzamide (**1a–d**) afforded **3aa** in 68% yield.

To study the reactivity of this catalytic system, several control experiments were conducted (Scheme 4). The reaction between *N*-methylaniline, a leaving group of **1a**, and *N*-phenylbenzamide, did not yield any product. This result implies that the reverse reaction is not favored under standard conditions. A competitive experiment between two different benzamides, with either electron-withdrawing or electron-donating substituents, was conducted using 4-methoxyaniline under standard conditions to provide **3de** and **3he** in 15% and 22% yields, respectively. Similarly, a competitive experiment between two different anilines **2e** and **2g** was conducted. 4-Methoxyaniline and 4-fluoroaniline afforded **3ae** and **3ag** in 45% and 25% yields, respectively. These results suggest that benzamides bearing electron-withdrawing substituents are more active than those with electron-donating groups, and that anilines substituted with electron-donating groups are more active than those having electron-withdrawing groups.



Scheme 4 Control experiments.

Conclusions

In summary, unactivated tertiary amides, such as *N*-methyl-*N*-phenylbenzamide, reacted with primary amines in the presence of $NiCl_2$ and a briphos ligand to deliver transamidated secondary amides in good yields. The employment of $NiCl_2$ has several advantages, as it is an inexpensive and easily handled reagent. Among the briphos ligands, *N*-3,5-dimethoxyphenyl substituted briphos having a *tert*-butyl substituent at the phenol moiety, **L4**, provided optimal results. It was found that briphos ligands bearing electron-donating groups and sterically bulky substituents exhibited superior activity compared to other briphos ligands. We believe that the steric bulkiness of the ligands plays a major role in improving the reactivity of the Ni catalysts. Accordingly, *tert*-butyl substituted briphos ligands **L3**, **L4**, and **L6** showed better reactivity than the non-substituted briphos ligands **L1**, **L2**, and **L5**. Among *tert*-butyl substituted briphos ligands, electronic tuning was achieved with methoxy groups, showing that **L4** is the optimal ligand. We will not discuss the detailed ligand effect further at this moment, but will continue to investigate the reaction mechanism to completely understand the ligand effect. Aromatic amines, including heteroaromatic amines, benzyl amines, and alkyl amines, afforded the transamidated products in moderate to good yields. Various substituted *N*-methyl-*N*-phenylbenzamides displayed good activity in the transamidation of aniline.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This research was supported by a National Research Foundation of Korea (NRF) grant funded by the Korea government (NRF-2012M3A7B4049655 and 2020R1A2C2013420). The spectral data were obtained from the Gwangju Center of Korea Basic Science Institute.

Notes and references

1 (*a*) D. Whitford, *Proteins: Structure and Function Wiley*, New York, 2005; (*b*) N. Sewald and H.-D. Jakubke, *Peptides: Chemistry and Biology Wiley*, New York, 2009; (*c*) V. R. Pattabiraman and J. W. Bode, *Nature*, 2011, **480**, 471–479; (*d*) L. Baibaut, N. Ollivier and O. Melnyk, *Chem. Soc. Rev.*, 2012, **41**, 7001–7015; (*e*) J.-S. Zheng, S. Tang, Y.-C. Huang and L. Liu, *Acc. Chem. Res.*, 2013, **46**, 2475–2484.

2 (*a*) J. S. Carey, D. Laffan, C. Thomson and M. T. Williams, *Org. Biomol. Chem.*, 2006, **4**, 2337–2347; (*b*) T. Cupido, J. Tulla-Puche, J. Spengler and F. Albericio, *Curr. Opin. Drug Discovery Dev.*, 2007, **10**, 768–783; (*c*) J. A. Aubé, *Angew. Chem., Int. Ed.*, 2012, **51**, 3063–3065; (*d*) E. Armelin, L. Franco, A. Rodriguez-Galan and J. Puiggali, *Macromol. Chem. Phys.*, 2002, **203**, 48–58; (*e*) K. Marchildon, *Macromol. React. Eng.*, 2011, **5**, 22–54.

3 C. L. Allen and J. M. J. Williams, *Chem. Soc. Rev.*, 2011, **40**, 3405–3415.

4 (*a*) H. Lundberg, F. Tinnis, N. Selander and H. Adolfsson, *Chem. Soc. Rev.*, 2014, **43**, 2714–2742; (*b*) J. R. Dunetz, J. Magano and G. A. Weisenburger, *Org. Process Res. Dev.*, 2016, **20**, 140–177.

5 K. Ekoue-Kovi and C. Wolf, *Chem. – Eur. J.*, 2008, **14**, 6302–6305.

6 (*a*) S.-I. Murahashi, T. Naota and E. Saito, *J. Am. Chem. Soc.*, 1986, **108**, 7846–7847; (*b*) C. L. Allen, A. A. Lapkin and J. M. J. Williams, *Tetrahedron Lett.*, 2009, **50**, 4262–4264.

7 (*a*) A. Schoenberg and R. F. Heck, *J. Org. Chem.*, 1974, **39**, 3327–3331; (*b*) K. Kumar, A. Zapf, D. Michalik, A. Tillack, T. Heinrich, H. Böttcher, M. Arlt and M. Beller, *Org. Lett.*, 2004, **6**, 7–10; (*c*) A. Brennführer, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2009, **48**, 4114–4133.

8 (*a*) R. M. Lanigan and T. D. Sheppard, *Eur. J. Org. Chem.*, 2013, **2013**, 7453–7465; (*b*) S. Adachi, N. Kumagai and M. Shibasaki, *Tetrahedron Lett.*, 2018, **59**, 1147–1158; (*c*) W. Guo, J. Huang, H. Wu, T. Liu, Z. Luo, J. Jian and Z. Zeng, *Org. Chem. Front.*, 2018, **5**, 2950–2954; (*d*) H. Wu, W. Guo, S. Daniel, Y. Li, C. Liu and Z. Zeng, *Chem. – Eur. J.*, 2018, **24**, 3444–3447; (*e*) L. Xiong, R. Deng, T. Liu, Z. Luo, Z. Wang, X.-F. Zhu and Z. Zeng, *Adv. Synth. Catal.*, 2019, **361**, 5383–5391.

9 (*a*) S. K. Davidsen, P. D. May and J. B. Summers, *J. Org. Chem.*, 1991, **56**, 5482–5485; (*b*) E. Bon, E. C. H. Bigg and G. Bertrand, *J. Org. Chem.*, 1994, **59**, 4035–4036; (*c*) T. A. Dineen, M. A. Zajac and A. G. Myers, *J. Am. Chem. Soc.*, 2006, **126**, 16406–16409; (*d*) M. Zhang, S. Imm, S. Bähn, L. Neubert, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2012, **51**, 3905–3909; (*e*) C. L. Allen, B. N. Atkinson and J. M. J. Williams, *Angew. Chem., Int. Ed.*, 2012, **51**, 1383–1386; (*f*) S. N. Rao, D. C. Mohan and S. Adimurthy, *Org. Lett.*, 2013, **15**, 1496–1499; (*g*) K. P. Patel, E. M. Gayakwad, V. V. Patil and G. S. Shankarling, *Adv. Synth. Catal.*, 2019, **361**, 2107–2116.

10 S. E. Eldred, D. A. Stone, S. H. Gellman and S. S. Stahl, *J. Am. Chem. Soc.*, 2003, **125**, 3422–3423.

11 (*a*) E. L. Baker, M. M. Yamano, Y. Zhou, S. M. Anthony and N. K. Garg, *Nat. Commun.*, 2016, **7**, 11554; (*b*) Y. Liu, S. Shi, M. Achtenhagen, R. Liu and M. Szostak, *Org. Lett.*, 2017, **19**, 1614–1617; (*c*) S. Shi and M. Szostak, *Chem. Commun.*, 2017, **53**, 10584–10587; (*d*) G. Meng, P. Lei and M. Szostak, *Org. Lett.*, 2017, **19**, 2158–2161; (*e*) G. Li and M. Szostak, *Nat. Commun.*, 2018, **9**, 4165; (*f*) A. Mishra, S. Singh and V. Srivastava, *Asian J. Org. Chem.*, 2018, **7**, 1600–1604; (*g*) M. M. Rahman, G. Li and M. Szostak, *J. Org. Chem.*, 2019, **84**, 12091–12100; (*h*) V. A. Fore and G. Maas, *Tetrahedron*, 2019, **75**, 3586–3595; (*i*) T. Zhou, G. Li, S. P. Nolan and M. Szostak, *Org. Lett.*, 2019, **21**, 3304–3309.

12 (*a*) G. Meng and M. Szostak, *Org. Lett.*, 2015, **17**, 4364–4367; (*b*) G. Meng and M. Szostak, *Angew. Chem., Int. Ed.*,

2015, **54**, 14518–14522; (*c*) Y. Liu, G. Meng, R. Liu and M. Szostak, *Chem. Commun.*, 2016, **52**, 6841–6844; (*d*) C. Liu and M. Szostak, *Chem. – Eur. J.*, 2017, **23**, 7157–7173; (*e*) M. M. Rahman, C. Liu, E. Biaz, B. Dziuk, R. A. Lalancette, Q. Wang, H. Chen, R. Szostak and M. Szostak, *J. Org. Chem.*, 2020, **85**, 5475–5485.

13 (*a*) J. M. Hoerter, K. M. Otte, S. H. Gellman, Q. Cui and S. S. Stahl, *J. Am. Chem. Soc.*, 2008, **130**, 647–654; (*b*) N. A. Stephenson, J. Zhu, S. H. Gellman and S. S. Stahl, *J. Am. Chem. Soc.*, 2009, **131**, 10003–10008.

14 C. W. Cheung, J.-A. Ma and X. Hu, *J. Am. Chem. Soc.*, 2018, **140**, 6789–6792.

15 G. Li, C.-L. Ji, X. Hong and M. Szostak, *J. Am. Chem. Soc.*, 2019, **141**, 11161–11172.

16 (*a*) S. Yu, T. Shin, M. Zhang, Y. Xia, H. Kim and S. Lee, *Org. Lett.*, 2018, **20**, 7563–7566; (*b*) J. Chen, M. Xu, S. Yu, Y. Xia and S. Lee, *Org. Lett.*, 2020, **22**, 2287–2292.

17 (*a*) T. Shin, H. Kim, S. Kim, A. Lee, M.-S. Seo, J. Choi, H. Kim and H. Kim, *Org. Lett.*, 2019, **21**, 5789–5791; (*b*) A. Lee and H. Kim, *J. Org. Chem.*, 2016, **81**, 3520–3527; (*c*) A. Lee and H. Kim, *J. Am. Chem. Soc.*, 2015, **137**, 11250–11253; (*d*) A. Lee, S. Ahn, K. Kang, M.-S. Seo, Y. Kim, W. Y. Kim and H. Kim, *Org. Lett.*, 2014, **16**, 5490–5493.