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Metal-free access to 3-allyl-2-alkoxychromanones *via* phosphine-catalyzed alkoxy allylation of chromones with MBH carbonates and alcohols†

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A metal-free access to 3-allyl-2-alkoxychromanones by PPh_3-catalyzed alkoxy allylation of chromones with MBH carbonates and alcohols is described. This reaction is performed under mild conditions and it shows good functional group tolerance, providing a series of functionalized chromanones in moderate to high yields with excellent diastereoselectivities. Deuterium-labeling experiments to probe a possible mechanism and scale-up reaction were also conducted.

Flavonoids are one of the largest and best investigated groups of plant secondary metabolites, which have shown a broad spectrum of biological activities.[1] Through searching the library of flavonoids, it was found that the 2-alkoxychromanone scaffold which contains an alkoxyl group at the 2-position of the basic structure of flavonoid exists in many biologically active natural products. As shown in Fig. 1, compound **I** is obtained from the seeds of *Psoralea corylifolia*.[2] Erigeroflavanone **II** isolated from *E. annuus* flowers exhibits inhibitory activities towards protein glycation and aldose reductase.[3] Compound **III** has been isolated from the leaves of *Cassia grandis* and it shows antioxidant and cytotoxic activities.[4] Apart from naturally occurring products, synthetic compounds also have potential biological applications. For instance, the synthetic 2-alkoxychromanones **IV** are potent and selective inhibitors of human and rat ecto-50-nucleotidase, alkaline phosphatases (TNAP and IAP) and ectonucleotidases.[5] In addition, the natural ferulenol **V** and the synthetic compounds **VI** were employed in the investigation of the structure–activity relationship, showing that the length of the isoprenyl side chain is important for the VKER inhibition compound.[6] Thus, it is of great importance to develop a synthetic method for this kind of chromanone derivative.

Allylic moieties are not only essential substructures in organic compounds but also versatile functional groups in organic synthesis.[7] To enrich the diversity of flavonoids, incorporation of allylic moieties into chromanones has become one of the efficient and useful strategies. In 2013, McErlean and co-workers reported an intramolecular vinylogous Stetter reaction of unsaturated ketones in the presence of triazolium salt and DBU, providing 3-allylchromanones in 70–88% yields with 84–96% ee.[8] In 2015, Jørgensen and co-workers synthesized branched and linear 3-allylchromans *via* an asymmetric γ-allylation of 2-(chroman-4-ylidene)acetaldehyde by combining organocatalysis and transition-metal catalysis.[9] Two years later, Song and co-workers disclosed an enantioselective protonation of silyl enol ethers catalyzed by Song's oligoEG catalyst with CsF as a fluoride source for access to 3-allylic chromanones and thiochromanones.[10] Although these elegant approaches to the synthesis of 3-allychromanones have been successfully established, the search for metal-free methods under mild conditions is highly desirable.

So far, significant progress has been made in organocatalyzed allylic alkylation reaction of MBH carbonates with

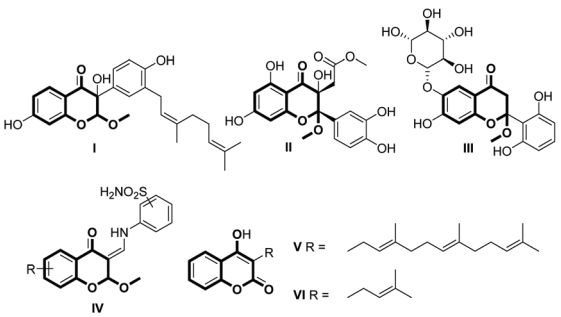

Fig. 1 Examples of biologically active compounds containing 2-alkoxyl or 3-allylchromanone cores.

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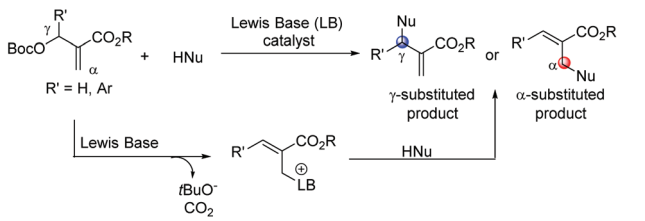
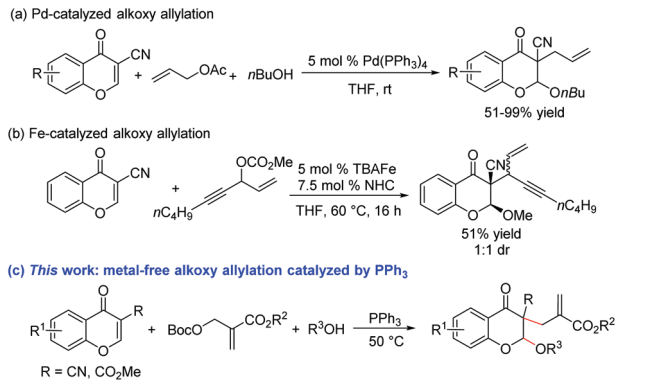
various nucleophiles (Scheme 1).[11] The plausible mechanism of the reaction is that a nucleophilic attack of a Lewis base (organocatalyst) on MBH carbonate takes place, releasing CO_2 and $(tBuO)^-$ anions that undergo hydrogen abstraction of the nucleophile. The nucleophilic anion attacks the allylic salt to generate a γ-substituted product. Alternatively, the nucleophilic anion attacks MBH carbonate *via* an S_N2' pathway or the allylic salt through an S_N2 pathway to give an α-substituted product. Thus, we expected that the allylic reaction of MBH carbonates with chromones could provide the corresponding 3-allyl-2-alkoxychromanone *via* a nucleophilic attack of the chromone-based nucleophile formed through a conjugate addition of the chromone with alcohol.

To the best of our knowledge, approaches to the synthesis of 3-allyl-2-alkoxychromanones are rare. In 2007, the Yamamoto group reported a palladium catalyzed three-component coupling reaction of chromones, allylic acetates and alcohols, generating a series of 3-allyl-2-alkoxychromanones in 51–99% yields (Scheme 2(a)).[12] In 2012, Plietker and co-workers reported a regioselective alkoxy allylation of activated olefins in the presence of an iron complex.[13] 3-Cyanochromone was also used as a substrate and the corresponding product was obtained in 51% yield with no selectivity (Scheme 2(b)). These reported methods for the synthesis of 3-allyl-2-alkoxychromanones are limited to transition metal catalysis, and organocatalysis has not been well developed. With the continuing work of our group in the synthesis of flavonoids,[14] we decided to investigate a phosphine-catalyzed alkoxy allylation of 3-cyanochromones with MBH carbonates and alcohols, which provides a metal-free access to a series of 3-allyl-2-alkoxychromanones (Scheme 2(c)).



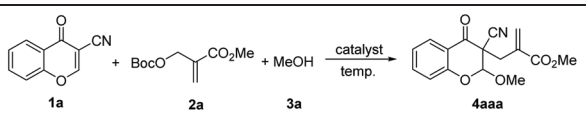
Scheme 1 Allylic alkylations of MBH carbonates with nucleophiles and the proposed mechanism.



Scheme 2 Synthesis of 3-allyl-2-alkoxychromanones.

We began our investigation by using 3-cyanochromone and unsubstituted MBH carbonate as model substrates. In light of the initial results (see the ESI†), different symmetric phosphines were tested and the results are shown in Table 1. 20 mol% of the commonly used weak nucleophilic PPh_3 resulted in the targeted product in 95% yield at room temperature (entry 1). When tricyclohexylphosphine and triisopropylphosphine were used as catalysts, the conversion of the reaction was low and the desired products were obtained in 35% and 18% yields, respectively (entries 2 and 3). This might be attributed to the poor leaving ability of these two phosphines, albeit with good donating ability. The reaction gave a full conversion but only 12% yield of the desired product in the presence of DPPE, accompanying an unrecognized by-product generated in the reaction (entry 4). Monophosphine XPhos furnished the product in 78% yield while bisphosphine *rac*-BIPHEP showed lower reactivity with 51% yield (entries 5 and 6). Notably, all the catalysts provided high diastereoselectivities (>20 : 1). Thus, PPh_3 was identified as the best catalyst (entry 1). Next examinations of catalyst loading and reaction temperature were performed. When the reaction was carried out at room temperature, lowering the catalyst loading led to incomplete conversions, hence the observation of decreased yields from 95% to 64% (entry 1 and entries 7 and 8). In contrast, an increase in reactivity from 74% to 98% was observed when the reactions were performed with the catalyst loading varying from 20 mol% to 5 mol% (entries 9–11), accompanied by the formation of an undetermined byproduct. Further decreasing the catalyst loading led to lower yields of the products which

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst	Cat. loading	Temp.	Yield[b]
1	PPh_3	20 mol%	rt	95
2	PCy_3	20 mol%	rt	35
3	$P(iPr)_3$	20 mol%	rt	18
4	DPPE	20 mol%	rt	12
5	XPhos	20 mol%	rt	78
6	BIPHEP	20 mol%	rt	51
7	PPh_3	10 mol%	rt	89
8	PPh_3	5 mol%	rt	64
9	PPh_3	20 mol%	50	74
10	PPh_3	10 mol%	50	82
11	PPh_3	5 mol%	50	98
12	PPh_3	2.5 mol%	50	91
13	PPh_3	1 mol%	50	90

[a] Unless otherwise specified, all the reactions were carried out with **1a** (0.2 mmol) and **2a** (0.3 mmol) in methanol (2.0 mL) in the presence of a catalyst at a specific temperature for 12–24 h. The diastereomeric ratio (dr) was determined by crude ^1H NMR spectroscopy. All the examples were with >20 : 1 dr. [b] Isolated yield.

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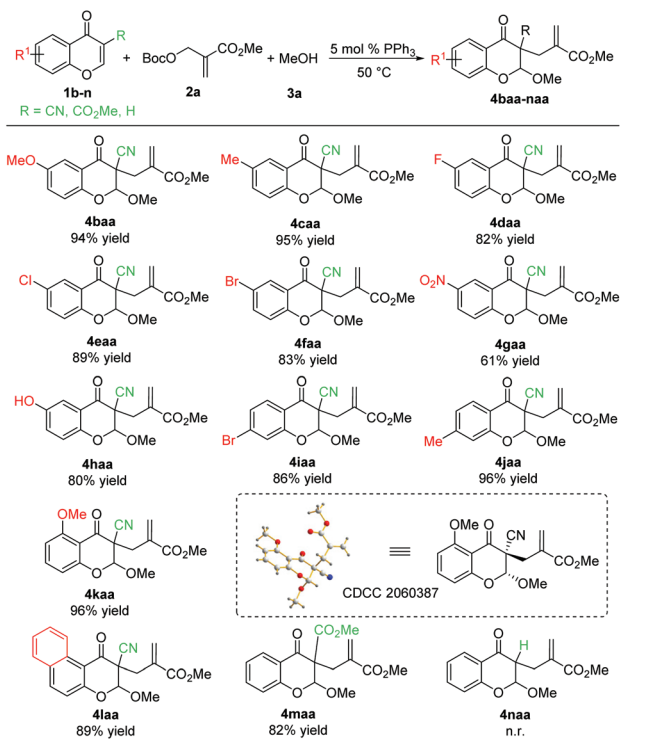
may be because the reduced catalyst loadings cannot promote the reaction as effectively as that with 5 mol% catalyst (entries 12 and 13). Finally, we chose the reaction conditions shown in entry 11 as the optimized conditions for further evaluation. The enantioselective version of the reaction was also investigated. Various chiral organocatalysts including bifunctional phosphines and cinchonidine-derived catalysts were employed in the reactions of 3-cyanochromones, unsubstituted MBH carbonates and methanol as solvent. Disappointingly, no or only trace enantioselectivity was observed (Scheme S1(a)†).

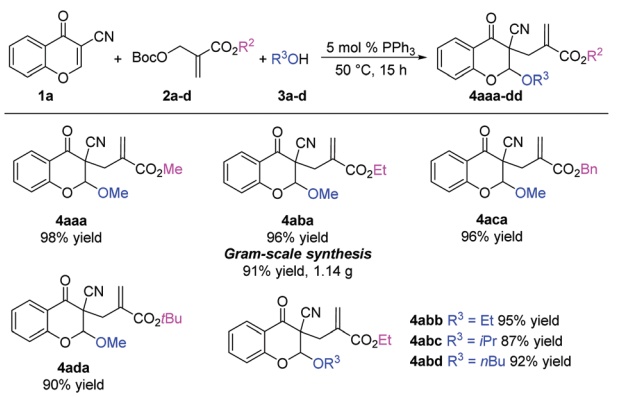
With the optimized reaction conditions in hand, the substrate scope of 3-cyanochromones was then explored to evaluate the efficiency of the catalytic system (Scheme 3). Generally, 3-cyanochromones containing electron-donating groups provided higher reactivities than those bearing electron-withdrawing groups (**4baa–caa** (94–95% yields) *vs.* **4daa-faa** (82–89% yields)). 3-Cyanochromone incorporated with a strong electron-withdrawing group (–NO_2) showed decreased reactivity, and the targeted product **4gaa** was obtained in only 61% yield. The reaction could also proceed smoothly when there is an unprotected hydroxyl group at the 6-position of 3-cyanochromone, generating the product **4haa** in 80% yield. The position of the substituent on the benzene ring of 3-cyanochromone has no significant impact on the reactivity of the reaction, and the corresponding chromanones were generated in 86–96% yields (**4iaa–kaa**). Naphthalene-containing chromone furnished **4laa** in 89% yield. 3-Ester substituted chromone also worked well to give the desired product **4maa** in 82% yield. Chromone without a cyano group at the 3-position showed no reactivity under the current catalytic system (**4naa**). To our delight, all the examples gave high diastereoselectivities (>20 : 1). Besides, the relative configuration of the major diastereoisomer was unambiguously determined by single crystal X-ray diffraction of the product **4kaa** (CCDC 2060387†),[15] and the two newly formed bonds were found to be *trans* to each other.

Next, we tested the scope of MBH carbonates under the standard reaction conditions (Scheme 4). When MBH carbonates bearing different ester groups (CO_2Me, CO_2Et, CO_2Bn, and CO_2tBu) were employed as substrates, the corresponding chromanones (**4aaa–da**) were furnished in good to excellent yields (90–98%). The bulky group (CO_2tBu) slightly decreased the reactivity of the reaction. The reactions can take place successfully in the solvents ethanol, isopropanol and butanol, providing the targeted products in 87–95% yields (**4abb–d**). We also examined the phenyl substituted MBH carbonate. The α-regioselective product was obtained as a major product with 1 : 4 diastereoselectivity (Scheme S1(b)†). Other Brønsted acids, such as phenol, thiophenol, phenylmethanol, phenylacetylene and acetic acid, also have been tested. However, no desired product was obtained, and only the [3 + 2] cycloaddition products were observed. Besides, a gram-scale reaction was performed in the presence of 5 mol% PPh_3. The 3-cyanochromone **1a** (685 mg, 4 mmol) reacted with the MBH carbonate **2b** (1.38 g, 6 mmol) in methanol, providing the targeted product **4aba** in 91% yield (1.14 g) with >20 : 1 diastereoselectivity after 12 hours. No significant loss in the yield and diastereomeric ratio was observed when compared with 0.2 mmol scale reaction (Scheme 4).

To gain insight into the mechanism, deuterium-labeling experiments were carried out (Scheme 5). As shown in Scheme 5(a), the 3-allyl-2-methoxychromanone **4aba** was dissolved in the solvent tetradeuteromethanol. No isotopic



Scheme 3 Scope of 3-cyanochromones. Reactions were carried out with **1b–n** (0.2 mmol) and **2a** (0.3 mmol) with 5 mol% PPh_3 in methanol (2.0 mL) at 50 °C for 12–36 h. The dr was determined by crude ^{1}H NMR spectroscopy. All examples were with >20 : 1 dr. Isolated yields were provided.



Scheme 4 Scope of MBH carbonates and alcohols. Reactions were carried out with **1a** (0.2 mmol) and **2a–d** (0.3 mmol) with 5 mol% PPh_3 in alcohol **3a–d** (2.0 mL) at 50 °C for 12–36 h. The dr was determined by crude ^{1}H NMR spectroscopy. All examples were with >20 : 1 dr. Isolated yields were provided.

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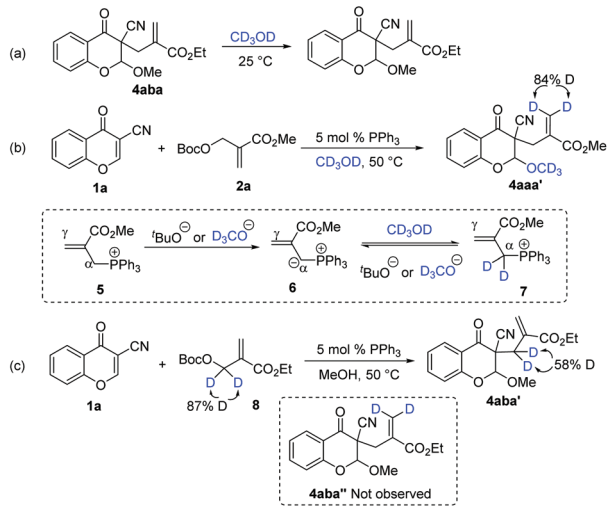
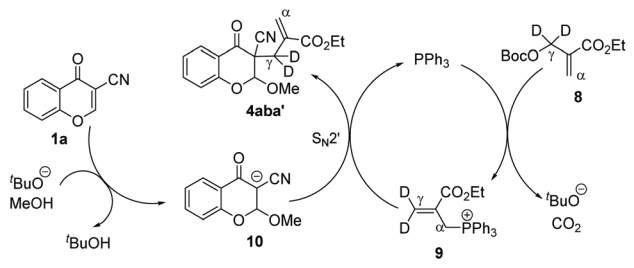


Scheme 5 Deuterium-labeling experiments.

exchange was observed, indicating that the final product has no active hydrogen that can conduct the hydrogen exchange process. When methanol-d4 was used as solvent, the hydrogens on the double bond of the allylic moiety of the product were deuterated, which shows that hydrogen exchange occurs between alcohol and phosphonium **5** (Scheme 5(b)). The phosphonium **5** can be deprotonated by *tert*-butoxy or methoxy anions, and the resulting phosphorus ylide **6** is protonated quickly by methanol-d4 to form the species **7**. On the other hand, the nucleophilic attack of the methoxy anion on 3-cyanochromone **1a** is much faster than that of the phosphorus ylide **6**. Thus, the 3-allyl-2-methoxychromanone **4aaa′** is the major product observed in the reaction. Finally, we synthesized and employed the deuterated MBH carbonate **8** in the alkoxy allylation (Scheme 5(c)). The deuterium only appeared in the methylene group of the product **4aba′**, and the product **4aba″** was not observed, suggesting that the nucleophilic addition of 3-cyano-2-methoxy-4-oxochroman-3-ide to phosphonium occurs *via* an S_N2' pathway rather than an S_N2 pathway. The possibility of nucleophilic addition of 3-cyano-2-methoxy-4-oxochroman-3-ide to MBH carbonate to form the product can also be excluded.

On the basis of the above experimental results, a mechanism for the alkoxy allylation of 3-cyanochromones with MBH carbonates was proposed as shown in Scheme 6. The reaction is initiated by the formation of the phosphonium **9**. Then, the released $(t\text{BuO})^-$ anion abstracts a proton from alcohol, generating an alkoxy anion that undergoes conjugate addition to 3-cyanochromone **1a** to form the nucleophilic species **10**. Finally, an S_N2' nucleophilic addition of 3-cyano-2-methoxy-4-oxochroman-3-ide **10** to the phosphonium **9** takes place, releasing the final product **4aba′** and regenerating the catalyst.



Scheme 6 Proposed mechanism.

Conclusions

In summary, phosphine-catalyzed alkoxy allylation of 3-cyanochromones with MBH carbonates and alcohols has been developed under mild reaction conditions, providing a metal-free access to various 3-allyl-2-alkoxychromanones in good to high yields with excellent diastereoselectivity. The deuterium experiments demonstrate that the reaction takes place *via* an S_N2' nucleophilic addition of the formed 3-cyano-2-methoxy-4-oxochroman-3-ide to phosphonium rather than an S_N2 nucleophilic addition to phosphonium or an S_N2' nucleophilic addition to MBH carbonate. Other catalytic asymmetric transformations of chromones and MBH carbonates are currently underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 (*a*) *The Flavonoids: Advances in Research Since 1980*, ed. J. B. Harborne, Chapman and Hall, New York, 1988; (*b*) J. B. Harborne and C. A. Williams, *Nat. Prod. Rep.*, 1995, **12**, 639; (*c*) J. C. Le Bail, F. Varnat, J. C. Nicolas and G. Habrioux, *Cancer Lett.*, 1998, **130**, 209; (*d*) P. G. Pietta, *J. Nat. Prod.*, 2000, **63**, 1035; (*e*) *Flavonoids: Chemistry, Biochemistry and Applications*, ed. Ø. M. Andersen and K. R. Markham, Taylor & Francis, London, 2006.
2 S. Ma, Y. Huang, Y. Zhao, G. Du, L. Feng, C. Huang, Y. Li and F. Guo, *Phytochem. Lett.*, 2016, **16**, 213.
3 N. H. Yoo, D. S. Jang, J. L. Yoo, Y. M. Lee, Y. S. Kim, J. H. Cho and J. S. Kim, *J. Nat. Prod.*, 2008, **71**, 713.
4 N. M. Hegazi and A. N. Hashim, *Pharmazie*, 2016, **71**, 544.
5 M. al-Rashida, G. Batool, A. Sattar, S. A. Ejaz, S. Khan, J. Lecka, J. Sevigny, A. Hameed and J. Iqbal, *Eur. J. Med. Chem.*, 2016, **115**, 484.
6 M. Gebauer, *Bioorg. Med. Chem.*, 2007, **15**, 2414.

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7 B. M. Trost, L. Matthew and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921.
8 K. R. Law and C. S. McErlean, *Chem. – Eur. J.*, 2013, **19**, 15852.
9 L. Naesborg, K. S. Halskov, F. Tur, S. M. Monsted and K. A. Jorgensen, *Angew. Chem., Int. Ed.*, 2015, **54**, 10193.
10 S. Paladhi, Y. Liu, B. S. Kumar, M. J. Jung, S. Y. Park, H. Yan and C. E. Song, *Org. Lett.*, 2017, **19**, 3279.
11 Selected references: (*a*) H. L. Cui, X. Feng, J. Peng, J. Lei, K. Jiang and Y. C. Chen, *Angew. Chem., Int. Ed.*, 2009, **48**, 5737; (*b*) T. Furukawa, J. Kawazoe, W. Zhang, T. Nishimine, E. Tokunaga, T. Matsumoto, M. Shiro and N. Shibata, *Angew. Chem., Int. Ed.*, 2011, **50**, 9684; (*c*) F. Zhong, J. Luo, G. Y. Chen, X. Dou and Y. Lu, *J. Am. Chem. Soc.*, 2012, **134**, 10222; (*d*) J. Zhang, H. H. Wu and J. Zhang, *Org. Lett.*, 2017, **19**, 6080; (*e*) S. L. Li, C. Yang, Q. Wu, H. L. Zheng, X. Li and J. P. Cheng, *J. Am. Chem. Soc.*, 2018, **140**, 12836; (*f*) Z. Li, M. Frings, H. Yu, G. Raabe and C. Bolm, *Org. Lett.*, 2018, **20**, 7367; (*g*) Z. Li, M. Frings, H. Yu and C. Bolm, *Org. Lett.*, 2019, **21**, 3119; (*h*) P. Chen, Y. Li, Z. C. Chen, W. Du and Y. C. Chen, *Angew. Chem., Int. Ed.*, 2020, **59**, 7083; (*i*) G. Yang, H. Zheng, X. Li and J. Cheng, *ACS Catal.*, 2020, **10**, 2324; (*j*) H. Guo, Y. C. Fan, Z. Sun, Y. Wu and O. Kwon, *Chem. Rev.*, 2018, **118**, 10049; (*k*) H. Ni, W. L. Chan and Y. Lu, *Chem. Rev.*, 2018, **118**, 9344; (*l*) P. Xie and Y. Huang, *Org. Biomol. Chem.*, 2015, **13**, 8578.
12 N. T. Patil, Z. Huo and Y. Yamamoto, *Tetrahedron*, 2007, **63**, 5954.
13 A. P. Dieskau, M. S. Holzwarth and B. Plietker, *Chem. – Eur. J.*, 2012, **18**, 2423.
14 (*a*) Q. He, C. M. So, Z. Bian, T. Hayashi and J. Wang, *Chem. – Asian J.*, 2015, **10**, 540; (*b*) Q. Yang, S. Li and J. Wang, *Org. Chem. Front.*, 2018, **5**, 577; (*c*) L. Lyu, M. Y. Jin, Q. He, H. Xie, Z. Bian and J. Wang, *Org. Biomol. Chem.*, 2016, **14**, 8088; (*d*) L. Meng, M. Y. Jin and J. Wang, *Org. Lett.*, 2016, **18**, 4986; (*e*) L. Meng and J. Wang, *Synlett*, 2016, **27**, 656; (*f*) D. Xiong, W. Zhou, Z. Lu, S. Zeng and J. Wang, *Chem. Commun.*, 2017, **53**, 6844; (*g*) S. H. Luo, L. Meng, Q. X. Yang and J. Wang, *Synlett*, 2018, **29**, 2071; (*h*) Q. Yang, R. Guo and J. Wang, *Asian J. Org. Chem.*, 2019, **8**, 1742; (*i*) Q. Yang, Y. Wang, S. Luo and J. Wang, *Angew. Chem., Int. Ed.*, 2019, **58**, 5343; (*j*) Q. Yang, S. Li and J. Wang, *ChemCatChem*, 2020, **12**, 3202–3206; (*k*) L. Meng, K. Y. Ngai, X. Chang, Z. Lin and J. Wang, *Org. Lett.*, 2020, **22**, 1155; (*l*) X. Gu, L. Meng, M. Li and J. Wang, *Org. Chem. Front.*, 2021, DOI: 10.1039/D1QO00030F.
15 CCDC 2060387† (for **4kaa**) contains the supplementary crystallographic data for this paper. These data can be obtained *via* http://www.ccdc.cam.ac.uk/data_request/cif.