Chemical Science

EDGE ARTICLE



View Article Online

View Journal | View Issue

Check for updates

Cite this: Chem. Sci., 2021, 12, 11399

o All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 28th June 2021 Accepted 22nd July 2021 DOI: 10.1039/d1sc03517g

rsc.li/chemical-science

Introduction

With the development of transition metal catalysis, zwitterionic species possessing a π -allylmetal complex moiety, which could be generated from allylic alcohol derivatives in situ, have been extensively employed for the construction of enantioenriched cyclic frameworks.¹ The corresponding hetero 1,n-dipoles can be readily generated from various allylic alcohol-derived carbonate, carbamate, or ester derivatives.² In addition, allcarbon-based dipoles have also been well explored,3 and those having a palladium-trimethylenemethane (Pd-TMM) motif received special attention.⁴ While fruitful scaffolds have been constructed by using Pd-TMM 1,3-carbodipoles,5 1,4-carbodiploes from allylic carbonates, generally with two electronwithdrawing groups at the homoallylic position, could be efficiently utilised (Scheme 1a).6 However, despite the significant progress in this field, the substitution patterns of the TMM

"Key Laboratory of Drug-Targeting and Drug Delivery System of the Ministry of Education, West China School of Pharmacy, and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu 610041, China. E-mail: duweiyb@scu.edu.cn; ycchen@scu.edu.cn; Fax: +86 28 85502609

Combining palladium and ammonium halide catalysts for Morita-Baylis-Hillman carbonates of methyl vinyl ketone: from 1,4-carbodipoles to ion pairs[†]

Yang Yang,^a Bo Zhu,^a Lei Zhu, ^b Ying Jiang,^a Chun-Ling Guo,^b Jing Gu,^b Qin Ouyang, ^b*^b Wei Du*^a and Ying-Chun Chen ^b*^{ab}

Here we report that Morita-Baylis-Hillman carbonates from diverse aldehydes and methyl vinyl ketones can be directly utilised as palladium-trimethylenemethane 1,4-carbodipole-type precursors, and both reactivity and enantioselectivity are finely regulated by adding a chiral ammonium halide as the ion-pair catalyst. The newly assembled intermediates, proposed to contain an electronically neutral π allylpalladium halide complex and a reactive compact ion pair, efficiently undergo asymmetric [4 + 2] annulations with diverse activated alkenes or isatins, generally with high regio-, diastereo- and enantioselectivity, and even switchable regiodivergent or diastereodivergent annulations can be well realised by tuning the substrate or catalyst assemblies. An array of control experiments, including UV/Vis absorption study and density functional theory calculations, are conducted to rationalise this new double activation mode combining a palladium complex and an ammonium halide as an ion-pair catalyst.

(a) Representative Pd-TMM carbodipoles and control model



Scheme 1 Diverse catalytic strategies involved in various Pd-based dipole species.

^bCollege of Pharmacy, Third Military of Medical University, Chongqing 400038, China. E-mail: ouyangq@tmmu.edu.cn

[†] Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data for new compounds, NMR, HRMS spectra and HPLC chromatograms, and CIF files of enantiopure products CCDC 2073270 (3s), 2073271 (6g), 2073272 (9c), and 2073273 (14). CCDC 2073270-2073273. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1sc03517g

moiety are not expandable, and the 1,4-carbodipole precursors are generally limited to those possessing a gem-diactivated carbon centre to meet the required C–H acidity for deprotonation and stabilisation for anion intermediates. In addition, the stereocontrol for the related annulations usually relies on the selection of properly designed chiral P-centred ligands, generally with crowded architectures. Moreover, for more flexible 1,4dipoles, a $Pd(\pi)$ -coordination site (including carbonyl, ester, and pyridine) embedding in the substrates is necessary for achieving high levels of enantioselectivity, by forming six- or seven-membered $Pd(\pi)$ -ligated intermediates (Scheme 1a). As a result, the development of an alternative catalytic system, rather than a sole Pd-based chiral complex, would be desirable for the reactions of some challenging substrates.

It has been documented that adding nBu_4Cl (TBAC) could significantly enhance the [3 + 2] annulation reaction of Pd(\mathfrak{n})based 1,3-C,N-dipoles and activated alkenes, by possibly forming anionic Pd complexes (Scheme 1b, left).⁷ Ooi even designed a chiral BINOL-derived ammonium–phosphine hybrid ligand, which enabled fine stereocontrol in the construction of vicinal quaternary stereogenic centres in the annulation reaction of similar dipoles from oxazolidinones, *via* proposed doubly ionpairing intermediates (Scheme 1b, right).⁸ Nevertheless, combining the double activation catalysis of ammonium halides with Pd-TMM carbodipole chemistry and deeply understanding the relevant activation mechanism still remain to be elucidated.

Morita-Baylis-Hillman (MBH) adducts, easily accessible by condensation between activated alkenes and carbonyl compounds, have been explored in asymmetric allylic alkylation reactions by forming π -allylpalladium intermediates.⁹ Typical MBH adducts from β-keto esters have been recently employed as Pd-TMM-type 1,4-carbodipole precursors in asymmetric [4 + 2] annulations via the deprotonation strategy;^{6e} nevertheless, the common analogues derived from simple enones, such as methyl vinyl ketone (MVK), and with broader substitution patterns (Scheme 1c), are much more challenging for similar transformations, and no success has been achieved yet. It was proposed that the corresponding intermediates, either 1,4-carbodipoles I or Pd-ligated five-membered species II10 after the oxidative addition/deprotonation process, might encounter several disadvantages, such as low stability or poor reactivity; especially, the stereocontrol would be quite challenging because of the flexibility of the skeleton together with the long distance between the nucleophilic site and the chiral ligand. Therefore, we envisaged that the addition of ammonium halide salts, as ion-pair catalysts (IPCs),11 would result in the formation of ion-pairing intermediates III from unstable 1,4-carbodipole species I, which would be potentially helpful for the subsequent reaction: (1) the cationic π -allylpalladium moiety would be neutralised by the halide of the IPC, especially when Cl⁻ or Br⁻ is used as a strong coordination ligand;¹² (2) the formation of a compact chiral ion-pair would not only stabilise the labile enolate but also guarantee better reactivity and enantioselectivity in the initial key addition process; (3) the assembly and application of an individual chiral IPC and chiral ligand would be easily tunable, thus providing better synergistic

stereocontrol and potentially realising diastereodivergent synthesis in the annulations; (4) such a double activation catalytic strategy would be different from the previously reported cooperative catalytic mode combining palladium and phase-transfer catalysts (Scheme 1c).¹³

Results and discussion

Condition optimization

Based on the above considerations, we conducted the reaction of the MBH carbonate 1a condensed from MVK and benzaldehyde with 2-benzylidene-1H-indene-1,3(2H)-dione 2a under the catalysis of palladium. After extensive screening, it was found that the expected [4 + 2] spirocyclic product¹⁴ 3a with an exomethylene group could be efficiently obtained with exclusive regio- and diastereo-selectivity, by employing $Pd(OAc)_2$ and a bisphosphine ligand, such as BINAP L1 or SKP L2,^{9c} suggesting that 1,4-carbodipole I could be generated.^{6e} Unfortunately, very low enantiocontrol was observed, probably due to the remote reaction site (Table 1, entries 1 and 2). Phosphoramidite (R)-L3 was tested as well, but failed to afford any product (entry 3). We also tried the bifunctional ligand L4 bearing an ammonium salt,^{8a} without success either (entry 4). In contrast, when cinchonine-derived ammonium salt C1 was added into the previously inert palladium/achiral phosphoramidite L5 catalytic system, high reactivity, albeit with low enantiocontrol, was observed, suggesting the potential formation of a reactive ionpairing intermediate (entry 5). Chiral salts had apparent effects on both reactivity and enantioselectivity (entries 6-10), and C4 with a bulky substituent gave a higher ee value (entry 8).¹⁵ It should be noted that no reaction occurred without the phosphoramidite ligand even in the presence of C4 (entry 11). In contrast, the combination of a bisphosphine ligand L1 or L2 and C4 proved to be unsuccessful (entries 12 and 13). These results indicated that adding an ammonium halide would apparently change the previously formed Pd(II) species of 1a.¹⁰ Subsequently, a few chiral phosphoramidites were explored with chiral IPC C4. As a mismatch was observed for ligand (R)-L3 (entry 14), the enantioselectivity was slightly improved with (S)-L3 (entry 15). Moreover, better enantiocontrol was achieved by changing the N-substituent of the phosphoramidite to a bulkier one (entry 16), and the optimal results were obtained with L7 (entry 17). Meanwhile, the significance of IPC was further confirmed, since no reaction occurred without C4 (entry 18). Pleasingly, the reactivity and stereoselectivity were almost retained with lower loadings of the dipole precursor, chiral ligand and IPC (entry 19).10

Substrate scope of regioselective [4 + 2] annulations

With the optimal conditions in hand, we next explored the substrate scope of the asymmetric [4 + 2] annulations of MBH carbonates 1 and 2-alkylidene indene-1,3-diones 2 under the double activation catalysis of Pd(OAc)₂, ligand L7 and IPC C4. The results are summarised in Table 2. For MBH carbonates 1 derived from different aromatic aldehydes or cinnamaldehyde and MVK, good reactivity was observed even with 2.5 mol%

Table 1 Screening conditions of asymmetric [4 + 2] annulation between MBH carbonate 1a and activated alkene $2a^{a}$

 $\begin{array}{c} Boco \\ Ph \\ + \\ 1a \end{array} + \left(\begin{array}{c} \downarrow \\ 2a \end{array} \right)^{O} \\ Ph \\ L(10 \text{ mol}\%) \\ C(10 \text{ mol}$

Entry	Ligand	С	Time (h)	$\operatorname{Yield}^{b}(\%)$	ee ^c (%)
1	L1	_	24	86	-3
2	L2	_	24	77	6
3	(R)-L3	_	24	NR	_
4	L4	_	24	NR	_
5	L5	C1	39	95	-2
6	L5	C2	39	27	-9
7	L5	C3	39	74	39
8	L5	C4	18	70	81
9	L5	C5	39	87	50
10	L5	C6	39	<10	-17
11	_	C4	24	NR	_
12	L1	C4	24	NR	_
13	L2	C4	24	<5	_
14	(R)-L3	C4	6	46	70
15	(S)-L3	C4	6	63	86
16	L6	C4	22	63	91
17	L7	C4	36	86	93
18	L7	_	36	NR	_
19^d	L7	C4	36	83	92

^{*a*} Unless otherwise noted, reactions were carried out with MBH carbonate **1a** (0.075 mmol), acceptor **2a** (0.05 mmol), $Pd(OAc)_2$ (5 mol%), L (10 mol%) and C (10 mol%) in toluene (1.0 mL) under Ar. ^{*b*} Isolated yield. ^{*c*} Determined by HPLC analysis on a chiral stationary phase. ^{*d*} With **1a** (0.06 mmol), L7 (7.5 mol%) and C1 (7.5 mol%).

loadings of a palladium catalyst in some cases, and the corresponding products **3a-3p** were smoothly produced in high yields with excellent stereoselectivity (Table 2, entries 1–16). It should be noted that the halide substituents on the aryl ring could be well-tolerated. When acceptors **2** with a different aryl group were employed, similarly good results were generally obtained (entries 17–25). An alkyl-substituted substrate was also applicable albeit with moderate enantioselectivity (entry 26). In addition, product **3aa** with an additional stereogenic centre was afforded with good diastereoselectivity from a perillaldehydederived enone (entry 27).¹⁶ In some cases, using Pd(OAc)₂ showed low reactivity, and thus other palladium sources were applied for better results (entries **17**, 26 and 27).

Table 2Substrate scope of asymmetric [4 + 2] annulations betweenMBH carbonates 1 and alkenes 2^a

BocO´		Pd(OAc) ₂ (5 mo C4 (7.5 mol%) L7 (7.5 mol%) toluene, RT, 36 >19:1 dr	(%) $(%)$	
Entry	R^1	R ²	Yield ^{b} (%)	ee ^c (%)
1	Ph	Ph	3a , 83	92
2^d	$3-CH_3C_6H_4$	Ph	3b, 76	93
3^d	$4-CH_3C_6H_4$	Ph	3c, 78	93
1	$4\text{-PhC}_6\text{H}_4$	Ph	3d , 80	92
5	$4-FC_6H_4$	Ph	3e , 93	94
5 ^e	$3,4-Cl_2C_6H_3$	Ph	3f , 70	93
7 ^d	$2\text{-BrC}_6\text{H}_4$	Ph	3g , 94	92
3	$3-BrC_6H_4$	Ph	3h , 90	92
Θ^e	$4-BrC_6H_4$	Ph	3i , 89	89
10	$2-NO_2C_6H_4$	Ph	3j , 80	88
11	$4 - NO_2C_6H_4$	Ph	3k , 98	95
12	4-CNC ₆ H ₄	Ph	31 , 83	95
13	2-Naphthyl	Ph	3m , 84	92
14^e	2-Furyl	Ph	3n , 81	90
15^e	3-Furyl	Ph	30, 88	91
16	2-Styryl	Ph	3p , 75	92
17 ^f	Ph	$2-CH_3C_6H_4$	3q , 96	94
18^e	Ph	$4-CH_3C_6H_4$	3r , 90	93
19	Ph	$4-tBuC_6H_4$	3s , 90	93 ^g
20	Ph	3-MeOC ₆ H ₄	3t , 82	96
21	Ph	2-ClC ₆ H ₄	3u , 56	81
22	Ph	$4-FC_6H_4$	3v , 80	92
23	Ph	$4-BrC_6H_4$	3w , 77	95
24	Ph	$3-NO_2C_6H_4$	3x, 61	92
25	Ph	3-Furyl	3y , 93	85
26^h	Ph	Cyclopropanyl	3z, 96	61^i
27 ^h	Ph)♦٤-	3aa , 73	<i>j</i>

^{*a*} Unless otherwise noted, reactions were carried out with MBH carbonate **1** (0.12 mmol), alkene 2 (0.10 mmol), Pd(OAc)₂ (5 mol%), C4 (7.5 mol%) and L7 (7.5 mol%) in toluene (1.0 mL) at rt for 36 h under Ar. ^{*b*} Isolated yields. ^{*c*} Determined by HPLC analysis on a chiral stationary phase; generally dr > 19 : 1 by ¹H NMR analysis. ^{*d*} For 72 h. ^{*e*} With Pd(OAc)₂ (2.5 mol%), C4 (3.75 mol%) and L7 (3.75 mol%) in toluene (1.0 mL). ^{*f*} With Pd₂(dba)₃ (2.5 mol%). ^{*s*} The absolute configuration of enantiopure **3s** was determined by X-ray analysis. The other products were assigned by analogy. ^{*h*} With PdCp(η³-allyl) (5 mol%). ^{*i*} Dr = 15 : 1. ^{*j*} Dr = 8 : 1.

Remarkably, the MBH carbonate **1q** derived from ethyl glyoxalate and MVK was compatible as well in the reactions with alkenes **2** under the standard conditions, and other types of [4 + 2] products **4a–4e** with different regioselectivity were furnished, by switching the allylic alkylation step from **C3** to **C1** (Scheme 2, intermediate **III**), and probably the electronic effect of the substituents played a key role in the regioselectivity.¹⁰

Substrate scope of asymmetric diastereodivergent [4 + 2] annulations

It is interesting but challenging to switch the diastereoselectivity of the reactions by simply tuning the conditions, as chiral compound libraries with higher stereodiversity could be efficiently obtained from identical starting materials.¹⁷



Scheme 2 Regiodivergent [4 + 2] annulations between MBH carbonate 1q and alkenes 2.

Considering that two independent chiral sources were involved in the current catalytic system, we assumed that the diastereodivergent [4 + 2] annulations of MBH carbonates **1** might be realised. Although we failed to construct different diastereomers with 2-alkylidene indene-1,3-diones **2**, 3-vinyl oxindoles **5** possessing an ester or a benzoyl group could successfully act as the counterparts in the switchable diastereodivergent [4 + 2]annulations. Under the catalysis of Pd(OAc)₂, achiral ligand **L8** and IPC **C4**, the major diastereomers **6a–6g**, having three contiguous stereogenic centres, were generally separated directly in moderate yields with excellent enantioselectivity, as summarised in Scheme 3, though fair to moderate diastereocontrol was observed.¹⁰

In contrast, the assembly of $Pd(OAc)_2$, ligand (*R*)-L3 and chiral IPC C7 could switch the diastereoselectivity, and afford separable diastereomers **7a–7d** in moderate yields and enantioselectivity (Scheme 4, conditions A). Although we could not achieve more satisfactory results by screening diverse catalyst combinations,¹⁰ it was found that the substitution pattern of the acceptors also had a dramatic effect on the outcome. Almost enantiopure diastereomers **9a–h** were effectively isolated in moderate yields, by employing amide substrates **8** under the catalysis of $Pd(OAc)_2$, ligand (*S*)-L3 and chiral IPC **C4**, also demonstrating the flexibility and tunability of the current double activation catalytic system (Scheme 4, conditions B).¹⁰



Scheme 3 Asymmetric diastereodivergent [4 + 2] annulations between MBH carbonates 1 and 3-vinyl oxindoles 5.



Scheme 4 Asymmetric diastereodivergent [4 + 2] annulation by tuning the catalytic system or substrate.

Substrate scope of asymmetric oxa-[4 + 2] annulations

Besides activated alkenes, activated ketones, such as *N*-protected isatins 10,¹⁸ were applicable as two-atom partners in the asymmetric oxa-[4 + 2] annulations with MBH carbonate **1a**. As

Table 3 Asymmetric oxa-[4 + 2] annulations between MBH carbonate 1a and isatins 10^{a}



Entry	R^1	R ²	$\operatorname{Yield}^{b}(\%)$	ee ^c (%)
1	Ме	Н	11a , 62	87
2	Me	5-Me	11b , 72	90
3	Me	5-Cl	11c, 85	84
4	Me	6-Br	11d, 62	84
5	Me	7-Me	11e, 81 (72)	$92^{d}(91)$
6	Me	7-Cl	11f , 67	80
7	Bn	Н	11g , 78	80
8	Bn	5-Cl	11 h , 65	80

^{*a*} Unless otherwise noted, reactions were carried out with MBH carbonate **1** (0.12 mmol), isatin **10** (0.10 mmol), Pd(OAc)₂ (5 mol%), **C8** (7.5 mol%) and **L7** (7.5 mol%) in toluene (1.0 mL) at rt for 12 h under Ar. ^{*b*} Isolated yields. ^{*c*} Determined by HPLC analysis on a chiral stationary phase; dr > 19:1 by ¹H NMR analysis. ^{*d*} Data in parentheses were obtained on a 1.0 mmol scale. The absolute configuration of **11e** was determined by X-ray analysis after conversion to enantiopure **14** (Scheme 5). The other products were assigned by analogy.

summarised in Table 3, the assembly of Pd(OAc)₂, ligand L7 and IPC C8 proved to be a reliable catalytic system, giving spiro [tetrahydropyran-3,3'-oxindole] 11a-11h in moderate to good yields with good to high enantioselectivity (Table 3, entries 1-8), even on a 1.0 mmol scale (entry 5).10

Transformations of the [4 + 2] annulation products

The enone moiety in the products enables further transformations to access the products with higher molecular complexity. As illustrated in Scheme 5, the in situ generated 1,3dipole from N-phenylbenzohydrazonoyl chloride underwent highly diastereoselective [3 + 2] cycloaddition with 3a,¹⁹ affording the spirocyclic framework 12 in an excellent yield. In addition, the heterocycle 13 could be efficiently constructed with a retained ee value from 3a via a [4 + 2] annulation with malononitrile. In addition, an interesting dimerisation of 11e via an oxa-Diels-Alder reaction gave polycyclic product 14 with excellent diastereoselectivity and enantioselectivity.20

Mechanism studies

To gain some insight into the catalytic mechanism, several control experiments were further conducted. As summarised in Scheme 6a, the combination of Pd(OAc)₂ and achiral phosphoramidite L8 failed to promoted the reaction of 1a and 2a in the absence of an IPC. In contrast, adding either TBAC or TBAB significantly enhanced the desired annulation reaction, whereas the iodide salt (TBAI) was less efficient, probably due to the coordinating effects of different halides.12,21 While we were not able to obtain some valuable information by ¹H NMR or mass spectrometry analysis, we carried out UV-Vis absorption experiments to monitor the complexation process.²² As outlined in Scheme 6b, a slightly different absorption spectrum was observed after adding MBH carbonate 1a into the mixture of Pd(OAc)₂ and L8. In contrast, apparent absorption changes were detected by further adding diverse ammonium halides. In particular, much stronger absorption in the 320-380 nm area was observed, indicating that some new complex species would



1.8

Pd(OAc)a

Pd(OAc)₂ + L8 +

1a + TRA



Wavelength/nm

1.9

be generated from the previously formed dipole I or ligated intermediate II (Scheme 1c) and an ammonium halide.

In order to further rationalise the role of ammonium halides, the mechanism of the catalytic reaction was studied by density functional theory (DFT) calculations. To simplify the process, $P(OPh)_3$ was selected as the ligand, since it gave similar results to those of phosphoramidite L8,10 and simple Me₄NBr (TMAB) was employed as the PTC partner. As outlined in Scheme 7, after the oxidative insertion by Pd(0) and deprotonation, the fivemembered ligated intermediate DL-INT1-B was found to be the more stable intermediate.¹⁰ The reactive 1,4-carbodipole DL-**INT1-C** had a much higher energy (18.6 kcal mol^{-1}), and the subsequent addition to acceptor 2a via DL-TS1 had an energy barrier of 25.0 kcal mol⁻¹, which was found to be inert at room temperature (pathway A). In contrast, a ligand exchange of DL-INT1-B would easily occur after adding TMAB, giving intermediate INT1-B1-TMA1 (2.3 kcal mol⁻¹) (pathway B).²³ Moreover, isomerisation to active ion-pair INT1-D1-TMA1 after



Scheme 5 Synthetic transformations of the products.



Scheme 7 DFT calculations on the proposed catalytic mechanism, at the B3LYP-D3/6-311++G(d,p)//B3LYP-D3/6-31(d) SDD for the Pd (toluene) level.

Chemical Science

(12.9 kcal mol⁻¹) having an electronically neutral Pd(II) complex, the subsequent Michael addition to **2a** *via* **TS1** had an energy barrier of 20.4 kcal mol⁻¹, which was significantly lower than that of **DL-TS1**. The resultant **INT2** would be easily converted to the ion-pairing intermediate **INT3**, which would undergo allylic substitution *via* **TS2** with an energy barrier of 8.8 kcal mol⁻¹, finally affording the intermediate **INT4**. We also compared the possible formation of a regioisomer *via* **TS2'** from ion-pair **INT3'**, which had a higher energy barrier of 10.6 kcal mol⁻¹, also in good accordance with a predicted ratio (21 : 1). An obvious π - π interaction between the aromatic rings of **1a** and **2a** was observed in **TS2** (Scheme 7), which might be one of the reasons for the reduction of the energy and the formation of regioisomer **3a**.¹⁰

Conclusions

We have developed a new palladium/ammonium halide double activation catalytic system, which could facilitate the conversion of possible π -allylpalladium complex-based 1,4-carbodipoles from Morita-Baylis-Hillman (MBH) carbonates of vinyl methyl ketone to more reactive compact ion-pair species. Both palladium complex and ammonium halide components were easily tunable, which would be helpful for enhancing reactivity and stereocontrol on both nucleophilic and electrophilic sites of the newly formed intermediates in a cooperative manner. The catalytic efficacy of such a transition metal and organic ion-pair system has been well demonstrated in asymmetric [4 + 2] annulations of substantial MBH carbonates and 2-alkylidene indene-1,3-diones, affording densely functionalised spirocyclic compounds¹⁶ in moderate to good yields with excellent stereoselectivity, and even regioselective annulations could be switched by tuning the substitutions of the MBH carbonates. Furthermore, switchable diastereodivergent [4 + 2] annulations between MBH carbonates and 3-olefinic oxindoles have also been realised by modifying the flexible assembly of the palladium complex and ion-pairing agent. The catalytic system has been further utilised in asymmetric oxa-[4+2] annulations between MBH carbonates and isatins, affording an array of spiro[tetrahydropyran-3,3'-oxindole] architectures. Moreover, UV-Vis absorption experiments and DFT calculations have been conducted to elucidate the catalytic mechanism, especially for the possible role of ammonium halides. We believe that the flexible double activation system combining a palladium complex and an ion-pair catalyst would find more application in diverse asymmetric reactions.

Data availability

All experimental procedures, characterization, computational data, copies of NMR and HRMS spectra for all new compounds and HPLC chromatograms related to this study, can be found in the ESI.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for the financial support from the NSFC (21971166, 21931006, and 21921002) and National Key Research and Development Program of China (2018YFA0507900).

Notes and references

- 1 (a) N. De and E. J. Yoo, ACS Catal., 2018, 8, 48–58; (b)
 B. D. W. Allen, C. P. Lakeland and J. P. A. Harrity, Chem.-Eur. J., 2017, 23, 13830–13857; (c) T.-R. Li, Y.-N. Wang,
 W.-J. Xiao and L.-Q. Lu, Tetrahedron Lett., 2018, 59, 1521– 1530.
- 2 (a) F. Jiang, F.-R. Yuan, L.-W. Jin, G.-J. Mei and F. Shi, ACS Catal., 2018, 8, 10234–10240; (b) S. Singha, E. Serrano, S. Mondal, C. G. Daniliuc and F. Glorius, Nat. Catal., 2020, 3, 48–54; (c) T.-R. Li, F. Tan, L.-Q. Lu, Y. Wei, Y.-N. Wang, Y.-Y. Liu, Q.-Q. Yang, J.-R. Chen, D.-Q. Shi and W.-J. Xiao, Nat. Commun., 2014, 5, 5500–5509; (d) L. A. Leth, F. Glaus, M. Meazza, L. Fu, M. K. Thøgersen, E. A. Bitsch and K. A. Jørgensen, Angew. Chem., Int. Ed., 2016, 55, 15272– 15276; (e) Q. Cheng, H.-J. Zhang, W.-J. Yue and S.-L. You, Chem, 2017, 3, 428–436; (f) S. Singha, T. Patra, C. G. Daniliuc and F. Glorius, J. Am. Chem. Soc., 2018, 140, 3551–3554; (g) Z.-C. Chen, Z. Chen, Z.-H. Yang, L. Guo, W. Du and Y.-C. Chen, Angew. Chem., Int. Ed., 2019, 58, 15021–15025; (h) Y. Wei, S. Liu, M.-M. Li, Y. Li, Y. Lan, L.-Q. Lu and W.-J. Xiao, J. Am. Chem. Soc., 2019, 141, 133–137.
- 3 (a) B. M. Trost and Z. Zuo, Angew. Chem., Int. Ed., 2021, 60, 5806–5810; (b) B. M. Trost, P. J. Morris and S. J. Sprague, J. Am. Chem. Soc., 2012, 134, 17823–17831; (c) Q. Cheng, J.-H. Xie, Y.-C. Weng and S.-L. You, Angew. Chem., Int. Ed., 2019, 58, 5739–5743.
- 4 (*a*) B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 1–20; (*b*) B. M. Trost and G. Mata, *Acc. Chem. Res.*, 2020, **53**, 1293– 1305; (*c*) D. M. T. Chan, Recent Advances in Palladium-Catalyzed Cycloadditions Involving Trimethylenemethane and its Analogs, in *Cycloaddition Reactions in Organic Synthesis* ed. S. Kobayashi and K. A. Jørgensen, Wiley-VCH, Weinheim, 2002, pp. 57–83.
- 5 (a) B. M. Trost, Y. Wang and C. Hung, Nat. Chem., 2020, 12, 294–301; (b) B. M. Trost and Y.-L. A. Wang, Angew. Chem., Int. Ed., 2018, 57, 11025–11029; (c) B. M. Trost and G. Mata, Angew. Chem., Int. Ed., 2018, 57, 12333–12337; (d) Y.-Z. Liu, Z. Wang, Z. Huang, X. Zheng, W.-L. Yang and W.-P. Deng, Angew. Chem., Int. Ed., 2020, 59, 1238–1242.
- 6 (a) R. Shintani, S. Park and T. Hayashi, J. Am. Chem. Soc., 2007, 129, 14866–14867; (b) R. Shintani, M. Murakami and T. Hayashi, J. Am. Chem. Soc., 2007, 129, 12356–12357; (c) L.-C. Yang, Y.-N. Wang, R. Liu, Y. Luo, N. X. Qian, B. Yang, Z.-Q. Rong, Y. Lan, Z. Shao and Y. Zhao, Nat. Chem., 2020, 12, 860–868; (d) B. M. Trost, Z. Jiao, Y. Liu, C. Min and C.-I. Hung, J. Am. Chem. Soc., 2020, 142, 18628–18636; (e)

B. M. Trost and Z. Jiao, *J. Am. Chem. Soc.*, 2020, **142**, 21645–21650.

- 7 (a) J. G. Knight, P. A. Stoker, K. Tchabanenko, S. J. Harwood and K. W. M. Lawrie, *Tetrahedron*, 2008, 64, 3744–3750; (b)
 M. A. Lowe, M. Ostovar, S. Ferrini, C. C. Chen, P. G. Lawrence, F. Fontana, A. A. Calabrese and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2011, 50, 6370–6374.
- 8 (*a*) K. Ohmatsu, N. Imagawa and T. Ooi, *Nat. Chem.*, 2014, **6**, 47–51; (*b*) K. Ohmatsu, S. Kawai, N. Imagawa and T. Ooi, *ACS Catal.*, 2014, **4**, 4304–4306.
- 9 (a) B. M. Trost, H.-C. Tsui and F. D. Toste, J. Am. Chem. Soc., 2000, 122, 3534–3535; (b) X. Wang, F. Meng, Y. Wang, Z. Han, Y.-J. Chen, L. Liu, Z. Wang and K. Ding, Angew. Chem., Int. Ed., 2012, 51, 9276–9282; (c) X. Wang, P. Guo, Z. Han, X. Wang, Z. Wang and K. Ding, J. Am. Chem. Soc., 2014, 136, 405–411; (d) X. Wang, Z. Han, Z. Wang and K. Ding, Acc. Chem. Res., 2021, 54, 668–684; (e) X. Wang, X. Wang, Z. Han, Z. Wang and K. Ding, Angew. Chem., Int. Ed., 2017, 56, 1116–1119; (f) J. Liu, Z. Han, X. Wang, F. Meng, Z. Wang and K. Ding, Angew. Chem., Int. Ed., 2017, 56, 5050–5054.
- 10 For more details, see the ESI.†
- 11 (a) D. Qian and J. Sun, Chem.-Eur. J., 2019, 25, 3740-3751; (b)
 D. Uraguchi and T. Ooi, J. Synth. Org. Chem., Jpn., 2018, 76, 1144-1153; (c) L. Zong and C.-H. Tan, Acc. Chem. Res., 2017, 50, 842-856.
- 12 R. Jagadeesan, G. Velmurugana and P. Venuvanalingam, *RSC Adv.*, 2015, **5**, 80661–80667.
- 13 (a) G.-S. Chen, Y.-J. Deng, L.-Z. Gong, A.-Q. Mi, X. Cui, Y.-Z. Jiang, M. C. K. Choi and A. S. C. Chan, *Tetrahedron: Asymmetry*, 2001, **12**, 1567–1571; (b) M. Nakoji,

T. Kanayama, T. Okino and Y. Takemoto, *Org. Lett.*, 2001, 3, 3329–3331; (c) G.-Y. Ran, X.-X. Yang, J.-F. Yue, W. Du and Y.-C. Chen, *Angew. Chem., Int. Ed.*, 2019, **58**, 9210–9214.

- 14 D. Pizzirani, M. Roberti, S. Grimaudo, A. Di Cristina, R. M. Pipitone, M. Tolomeo and M. Recanatini, *J. Med. Chem.*, 2009, 52, 6936–6940.
- 15 Y. Yang, Y. Jiang, W. Du and Y.-C. Chen, *Chem.–Eur. J.*, 2020, **26**, 1754–1758.
- 16 Significant cytotoxic activity against the human gastric cancer cell line MGC803 was observed for some spirocyclic products **3**. See the ESI† for more details.
- 17 (a) S. Krautwald and E. M. Carreira, J. Am. Chem. Soc., 2017,
 139, 5627–5639; (b) M. Bihani and J. C. G. Zhao, Adv. Synth. Catal., 2017, 359, 534–575.
- 18 R. Shintani, S. Hayashi, M. Murakami, M. Takeda and T. Hayashi, Org. Lett., 2009, 11, 3754–3756.
- 19 Q.-Q. Yang, X. Yin, X.-L. He, W. Du and Y.-C. Chen, ACS Catal., 2019, 9, 1258–1263.
- 20 (a) D. Liao, H. Li and X. Lei, Org. Lett., 2012, 14, 18-21; (b)
 K. Fagnou and M. Lautens, Angew. Chem., Int. Ed., 2002, 41, 26-47.
- 21 A. Jutand, Appl. Organomet. Chem., 2004, 18, 574-582.
- 22 X. Huang, B. Wang, Y. Wang, G. Jiang, J. Feng and H. Zhao, *Nature*, 2020, **584**, 69–74.
- 23 The ammonium salt may be located at different positions, and thus computation work is too large to calculate each pose for different conformations with an ammonium salt. To evaluate the coordination models with **TMAB**, **PB-INT1-B1** and **PB-INT1-D1** were selected as the representative conformations for η^4 - and η^3 -complexation, respectively.