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Synthesis of New C_2-Symmetric Six-Membered NHCs and Their Application for the Asymmetric Diethylzinc Addition of Arylaldehydes

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Abstract: A concise method for the preparation of new 3,4,5,6-tetrahydropyrimidinium salts was presented in this paper. Further application of these salts in asymmetric diethylzinc addition of arylaldehydes was explored, giving the corresponding chiral second alcohols in good yields and moderate enantioselectivities.

Keywords: *N*-heterocyclic carbene; tetrahydropyrimidinium; enantioselectivity; asymmetric addition; chiral secondary alcohols

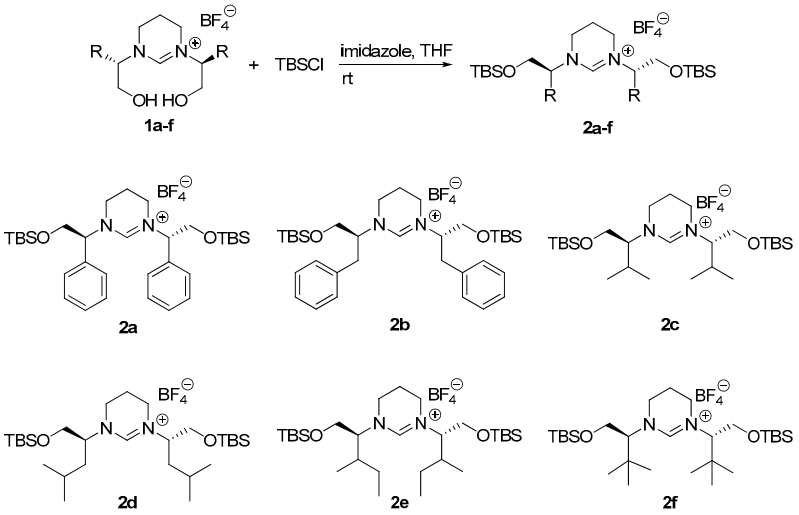
1. Introduction

Since Arduengo et al. reported the first isolation of stable *N*-heterocyclic carbene (NHCs) [1], this kind of ligand has attracted great interest, and tremendous success has been achieved in carbene chemistry [2–12]. Not surprisingly, great effort has been devoted to the design and development of efficient NHC ligands in past decades. These ligands, initially considered as mimics of phosphine [13], are now ubiquitous in organic chemistry because of their outstanding properties such as stronger σ-donor and weaker π-acceptor compared to the corresponding phosphane ligand, and the metal complexes of these ligands usually show better stability to moisture, air, and heat as well [14,15]. Naturally, the development of chiral NHCs and the application of these ligands in stereoselective catalysis are receiving considerable attention as a next step [16–21]. To date, most of the research has employed five-membered NHCs based on imidazole or imidazoline. The so-called "expanded-ring" NHCs with six- [22–37] and seven- [38–49] heterocyclic rings have recently attracted attention, as these "non-standard" NHCs show quite different properties, such as stronger basicity (nucleophilicity) and greater steric demand [50]. Structurally, the larger ring sizes of these unusual NHCs will lead to a comparatively large N–CNHC–N angle and consequential smaller C_{NHC}–N–C_R angle, which in turn results in better protection of metal centers and subsequently better performance in catalysis. As part of our ongoing interest in ring-expanded NHC chemistry [51,52], we here present the synthesis of C_2-symmetric six-membered NHCs precursors by a smooth three-step method. After deprotonation of the precursor salts in situ, the new six-membered NHCs were tested as catalysts in asymmetric diethylzinc addition of arylaldehydes, giving the corresponding secondary alcohol with good yields and moderate enantioselectivities.

2. Results

Using commercial available amino alcohols as a starting material, we synthesized a series of enantiopure 3,4,5,6-tetrahydropyrimidinium salts (**1a**–**1f**) incorporating two hydroxyl groups and

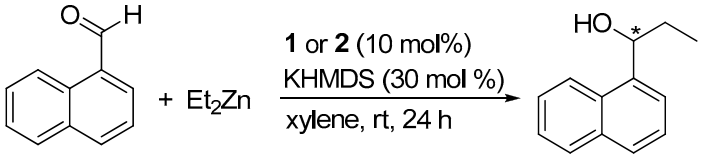
evaluated their efficiency as ligands in palladium-catalyzed deprotonative-cross-coupling processes (DCCP) [52]. However, these salts showed poor enantioselectivities when tested as catalysts in an asymmetric diethylzinc addition to aldehydes (Table 1, entries 1–6). Since a steric functional group around the carbene center may be beneficial for asymmetric catalysis, we were interested in preparing the derivatives of salts (**1**) by modification of the OH group with bulky silyl groups. As presented in Scheme 1, simple treatment of **1a**–**1f** with *tert*-butyldimethylsilyl chloride (TBSCl) gave silicification products **2a**–**2f** in good yields (76–94% yield, see Figure S1 in Supplementary Materials for NMR data of **2a**–**2f**).



Scheme 1. Synthesis of NHC precursors **2a**–**2f**.

The new precursor salts were then tested in enantioselective asymmetric diethylzinc addition to 1-naphthaldehyde (**3a**). As shown in Table 1, derivatives **2b**, **2e**, and **2f**, as catalysts in this transformation, showed better enantioselectivity than their parent compounds, and **2b** gave the best result (92% yield, 45% ee). Three new tetrahydropyrimidinium salts (Figure 1, **2g**–**2i**) were further prepared by the same method as shown in Scheme 1, with **1b** as a starting material. These salts replaced the OH group with different substituents. However, no improvement of ee values was observed when they were tested in this reaction (Table 1, entries 13–15). Next, we tried a variety of conditions with different solvents and bases. Unfortunately, no combination improved the enantioselectivity either (see Table S1 in Supplementary Materials for details).

Table 1. Comparison of NHC precursors.



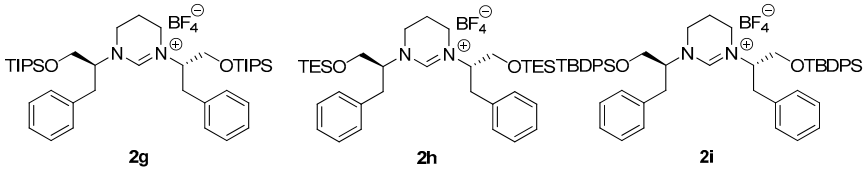
3a **4a**

Entry [a]	Salts	Yield (%) [b]	ee (%) [c]
1	**1a**	97	4
2	**1b**	86	13
3	**1c**	95	21
4	**1d**	90	5
5	**1e**	91	9
6	**1f**	77	1
7	**2a**	95	2

Table 1. *Cont.*

Entry [a]	Salts	Yield (%) [b]	ee (%) [c]
8	**2b**	92	45
9	**2c**	96	0
10	**2d**	95	1
11	**2e**	70	24
12	**2f**	89	11
13	**2g**	95	0
14	**2h**	97	6
15	**2i**	78	16

[a] Reaction condition: salt (10 mol %), $KN(SiMe_3)_2$ (30 mol %), Et_2Zn (2 equiv.), N_2, xylene, rt, 24 h. [b] Isolated yield. [c] Determined by chiral HPLC (CHIRALCEL OD Column) analysis.

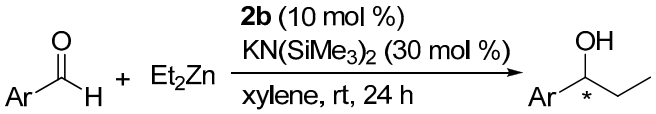


2g **2h** **2i**

Figure 1. The structures of **2g**–**2i**.

With **2b** as a catalyst precursor, different arylaldehydes were next applied in this transformation. As indicated in Table 2, the reaction proceeded well in most cases (67–95% yield). Arylaldehydes bearing electron-withdrawing (entries 3–9) and electron-donating (entries 10–13) groups, as well as heterocyclic substrates (entries 15–17), were all well-tolerated, giving product **4b**–**4r** in good yields and moderate enantiomeric excesses. The best enantioselectivity was obtained with nicotinaldehyde (**3p**) as a starting material, giving the product in 54% ee.

Table 2. Scope of methodology.



3 **4**

Entry [a]	Ar		Product	Yield (%) [b]	ee (%) [c]
1	2-Naphthyl	**3b**	**4b**	82	40
2	Ph	**3c**	**4c**	74	33
3	2-MePh	**3d**	**4d**	89	26
4	3,4-diMePh	**3e**	**4e**	78	40
5	2,4,6-triMePh	**3f**	**4f**	69	28
6	4-EtPh	**3g**	**4g**	86	37
7	2-MeOPh	**3h**	**4h**	92	35
8	3-MeOPh	**3i**	**4i**	81	38
9	4-MeOPh	**3j**	**4j**	73	28
10	2-FPh	**3k**	**4k**	88	14
11	4-FPh	**3l**	**4l**	79	28
12	4-CF_3Ph	**3m**	**4m**	95	48
13	3,5-diFPh	**3n**	**4n**	84	44
14	Cinnamyl	**3o**	**4o**	81	36
15	3-Pyridine	**3p**	**4p**	67	54
16	2-Thienyl	**3q**	**4q**	75	33
17	2-Quinolyl	**3r**	**4r**	87	29

[a] Reaction condition: **2b** (10 mol %), $KN(SiMe_3)_2$ (30 mol %), Et_2Zn (2 equiv.), N_2, xylene, rt, 24 h. [b] Isolated yield. [c] Determined by chiral HPLC (CHIRALCEL OD Column) analysis.

3. Materials and Methods

3.1. General

^{1}H- and ^{13}C-NMR spectra were obtained on Bruker AVANCE III 500 MHz and 600 MHz spectrometers (Bruker Co., Billerica, MA, USA) with TMS as the internal standard; MS spectra were measured on a Finnigan LCQDECA XP instrument and a Agilent Q-TOF 1290 LC/6224 MS system (Santa Clara, CA, USA); silica gel GF_{254} and H (10−40 mm, Qingdao Marine Chemical Factory, Qingdao, China) were used for TLC and CC. Unless otherwise noted, all reactions were carried out under an atmosphere of argon or nitrogen.

3.2. Preparation of Benzimidazolium Salt (**2**)

A mixture of **1a** (824 mg, 2 mmol), *tert*-butyldimethylsilyl chloride (1.2 g, 8 mmol) (Energy Chemical, Shanghai, China), and imidazole (1.09 g, 8 mmol) was dissolved in dry THF (10 mL). After stirring at room temperature for 12 h, the mixture was poured into water (50 mL) and extracted with dichloromethane (3 × 20 mL). The organic fractions were combined, washed with brine, and dried over Na_2SO_4 (Energy Chemical, Shanghai, China). The solvent was removed under reduced pressure, and the crude material purified by column chromatography (CH_2Cl_2/MeOH = 50/1) to give **2a** (1.06 g, 83%). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.44–7.35 (m, 10H), 4.97 (dd, J = 7.1, 3.9 Hz, 2H), 4.25–4.18 (m, 4H), 3.44–3.36 (m, 2H), 3.31–3.24 (m, 2H), 2.02–1.96 (m, 2H), 0.87 (s, 18H), 0.08 (s, 12H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 153.6, 133.7, 129.3, 129.2, 127.9, 68.6, 62.2, 41.3, 29.7, 25.8, 19.2, 18.1.

Analogous compounds **2b**–**2i** were prepared according to a procedure similar to that of **2a**. **2b**: 92% yield; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.32 (t, J = 7.4 Hz, 4H), 7.26 (d, J = 7.3 Hz, 2H), 7.18 (d, J = 7.2 Hz, 4H), 4.00 (s, 2H), 3.81–3.78 (m, 4H), 3.29 (m, 4H), 2.96 (dd, J = 7.8, 4.7 Hz, 4H), 1.77–1.70 (m, 2H), 0.90 (d, J = 4.9 Hz, 18H), 0.08 (s, 12H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 153.1, 136.1, 129.0, 127.2, 67.4, 64.0, 42.2, 34.7, 25.8, 18.9, 18.1. **2c**: 76% yield; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 3.87 (m, J = 11.6, 4.8 Hz, 4H), 3.58–3.51 (m, 2H), 3.44–3.35 (m, 4H), 2.13–2.01 (m, 4H), 1.02 (d, J = 6.6 Hz, 6H), 0.96 (d, J = 6.7 Hz, 6H), 0.88 (s, 18H), 0.08 (s, 12H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 154.0, 72.6, 62.3, 41.0, 26.4, 25.8, 19.8, 19.2, 19.1, 18.2. **2d**: 91% yield; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 3.85–3.78 (m, 4H), 3.71 (dd, J = 12.0, 7.5 Hz, 2H), 3.49 (m, 2H), 3.42 (m, 2H), 2.18 (s, 2H), 2.12–2.07 (m, 2H), 1.54–1.45 (m, 4H), 0.98 (dd, J = 6.3, 3.7 Hz, 12H), 0.89 (d, J = 6.8 Hz, 18H), 0.08 (s, 12H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 153.4, 64.8, 63.5, 41.6, 36.5, 25.8, 24.8, 22.7, 22.4, 19.1, 18.1. **2e**: 86% yield; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 3.92–3.84 (m, 4H), 3.59–3.45 (m, 4H), 3.40–3.33 (m, 2H), 2.10 (dd, J = 11.6, 5.7 Hz, 2H), 1.82 (dt, J = 10.0, 6.6 Hz, 2H), 1.38–1.33 (m, 2H), 1.20–1.17 (m, 2H), 0.97 (d, J = 6.6 Hz, 6H), 0.93 (t, J = 7.4 Hz, 6H), 0.90 (s, 18H), 0.08 (s, 12H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 154.1, 71.2, 62.3, 41.0, 32.5, 25.8, 25.5, 19.1, 18.2, 15.0, 10.8. **2f**: 94% yield; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 3.92 (d, J = 6.8 Hz, 4H), 3.55–3.46 (m, 6H), 2.13 (dd, J = 11.1, 5.5 Hz, 2H), 1.03 (s, 18H), 0.87 (s, 18H), 0.10 (s, 6H), 0.90 (s, 6H). **2g**: 73% yield; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.32 (t, J = 7.4 Hz, 4H), 7.25 (d, J = 7.0 Hz, 2H), 7.15 (d, J = 7.3 Hz, 4H), 3.97–3.79 (m, 4H), 3.45–3.23 (m, 4H), 3.07–2.85 (m, 4H), 1.79–1.74 (m, 2H), 1.03 (d, J = 6.5 Hz, 36H), 1.00 (m, 6H), 0.64 (m, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 153.1, 136.0, 129.1, 129.0, 127.3, 67.6, 64.9, 42.2, 34.7, 29.7, 18.0, 11.8. **2h**: 84% yield; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.32 (t, J = 7.4 Hz, 4H), 7.24 (t, J = 7.1 Hz, 2H), 7.19 (d, J = 7.1 Hz, 4H), 3.98 (tt, J = 8.3, 4.2 Hz, 2H), 3.85–3.73 (m, 4H), 3.37–3.22 (m, 4H), 3.03–2.90 (m, 4H), 1.73 (p, J = 5.7 Hz, 2H), 0.98–0.91 (m, 18H), 0.60 (q, J = 8.0 Hz, 12H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 153.0, 136.1, 129.1, 129.0, 128.8, 127.2, 67.5, 63.6, 42.3, 34.8, 29.7, 18.9, 6.8, 4.2. **2i**: 69% yield; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.61–7.56 (m, 8H), 7.47 (m, 4H), 7.41 (td, J = 7.2, 5.0 Hz, 8H), 7.24 (t, J = 7.4 Hz, 4H), 7.16 (t, J = 7.3 Hz, 2H), 7.10 (d, J = 7.1 Hz, 4H), 3.97 (d, J = 11.0 Hz, 2H), 3.88–3.79 (m, 4H), 3.29–3.13 (m, 4H), 2.95–2.83 (m, 4H), 1.70–1.64 (m, 2H), 1.07 (s, 18H); ^{13}C-NMR (125 MHz,

$CDCl_3$) δ 153.2, 135.7, 135.6, 135.5, 132.3, 130.2, 129.0, 128.9, 128.1, 128.0, 127.2, 67.3, 64.3, 41.6, 34.8, 29.7, 27.0, 19.2.

3.3. Representative Procedure for the Asymmetric Addition of Diethylzinc to Aldehyde

Under an argon atmosphere, a mixture of salt (**2b**) (0.01 mmol) and KN $(SiMe_3)_2$ (0.03 mmol) in xylene (1 mL) was stirred for 5 min at room temperature. Then diethylzinc (0.2 mmol) was added dropwise, followed by an addition of 1-naphthaldehdye (**3a**; 14 µL, 0.1 mmol). Upon stirring for 24 h at room temperature, the reaction was quenched by HCl (1 M, 1.0 mL) and extracted with Et_2O (3 × 2 mL). The combined organic phases were washed with water and dried over Na_2SO_4 and concentrated under vacuum. The residue was further purified by column chromatography (silica gel, hexane/AcOEt) to yield product **4a** as a colorless oil (92% yield, 45% ee). The spectral data were comparable to those reported [53]. The ee was determined by HPLC analysis with Daicel Chiralcel OD-H (hexane/^{i}PrOH = 90/10, flow rate = 0.5 mL/min, t_r (minor) = 15.7 min, t_r (major) = 28.6 min).

Analogous compounds **4b**–**4r** were prepared according to a procedure similar to that of **4a**. **4b**: 82% yield, 40% ee; the spectral data were comparable to those reported [53]. The ee was determined by HPLC analysis with Daicel Chiralcel OD-H (hexane/^{i}PrOH = 90/10, flow rate = 0.5 mL/min, t_r (minor) = 19.1 min, t_r (major) = 22.4 min). **4c**: 74% yield, 33% ee; the spectral data were comparable to those reported [53]. The ee was determined by HPLC analysis with Daicel Chiralcel OD-H (hexane/^{i}PrOH = 90/10, flow rate = 0.5 mL/min, t_r (minor) = 11.3 min, t_r (major) = 12.2 min). **4d**: 89% yield, 26% ee; the spectral data were comparable to those reported [53]. The ee was determined by HPLC analysis with Daicel Chiralcel OD-H (hexane/^{i}PrOH = 90/10, flow rate = 0.5 mL/min, t_r (minor) = 11.3 min, t_r (major) = 12.7 min). **4e**: 78% yield, 40% ee; the spectral data were comparable to those reported [53]. The ee was determined by HPLC analysis with Daicel Chiralcel OD-H (hexane/^{i}PrOH = 90/10, flow rate = 0.4 mL/min, t_r (major) = 14.5 min, t_r (minor) = 16.6 min). **4f**: 69% yield, 28% ee; the spectral data were comparable to those reported [53]. The ee was determined by HPLC analysis with Daicel Chiralcel OD-H (hexane/^{i}PrOH = 90/10, flow rate = 0.5 mL/min, t_r (minor) = 12.2 min, t_r (major) = 13.1 min). **4g**: 86% yield, 37% ee; the spectral data were comparable to those reported [53]. The ee was determined by HPLC analysis with Daicel Chiralcel OD-H (hexane/^{i}PrOH = 90/10, flow rate = 0.4 mL/min, t_r (major) = 8.6 min, t_r (minor) = 9.2 min). **4h**: 92% yield, 35% ee; the spectral data were comparable to those reported [53]. The ee was determined by HPLC analysis with Daicel Chiralcel OD-H (hexane/^{i}PrOH = 90/10, flow rate = 0.5 mL/min, t_r (major) = 13.6 min, t_r (minor) = 15.4 min). **4i**: 81% yield, 38% ee; the spectral data were comparable to those reported [53]. The ee was determined by HPLC analysis with Daicel Chiralcel OD-H (hexane/^{i}PrOH = 90/10, flow rate = 0.5 mL/min, t_r (minor) = 18.9 min, t_r (major) = 21.5 min). **4j**: 73% yield, 28% ee; the spectral data were comparable to those reported [53]. The ee was determined by HPLC analysis with Daicel Chiralcel OD-H (hexane/^{i}PrOH = 90/10, flow rate = 0.5 mL/min, t_r (minor) = 10.6 min, t_r (major) = 12.4 min). **4k**: 88% yield, 14% ee; the spectral data were comparable to those reported [53]. The ee was determined by HPLC analysis with Daicel Chiralcel OD-H (hexane/^{i}PrOH = 90/10, flow rate = 0.5 mL/min, t_r (major) = 11.7 min, t_r (minor) = 15.0 min). **4l**: 79% yield, 28% ee; the spectral data were comparable to those reported [53]. The ee was determined by HPLC analysis with Daicel Chiralcel OD-H (hexane/^{i}PrOH = 93/7, flow rate = 0.5 mL/min, t_r (major) = 11.1 min, t_r (minor) = 12.3 min). **4m**: 95% yield, 48% ee; the spectral data were comparable to those reported [53]. The ee was determined by HPLC analysis with Daicel Chiralcel OD-H (hexane/^{i}PrOH = 90/10, flow rate = 0.5 mL/min, t_r (major) = 7.7 min, t_r (minor) = 8.6 min). **4n**: 84% yield, 44% ee; the spectral data were comparable to those reported [53]. The ee was determined by HPLC analysis with Daicel Chiralcel OD-H (hexane/^{i}PrOH = 93/7, flow rate = 0.5 mL/min, t_r (major) = 11.6 min, t_r (minor) = 14.8 min). **4o**: 81% yield, 36% ee; the spectral data were comparable to those reported [53]. The ee was determined by HPLC analysis with Daicel Chiralcel OD-H (hexane/^{i}PrOH = 93/7, flow rate = 0.5 mL/min, t_r (major) = 12.8 min, t_r (minor) = 15.6 min). **4p**: 67% yield, 54% ee; the spectral data were comparable to those reported [53]. The ee was determined

by HPLC analysis with Daicel Chiralcel OD-H (hexane/^{i}PrOH = 93/7, flow rate = 0.5 mL/min, t_r (minor) = 12.9 min, t_r (major) = 14.1 min). **4q**: 75% yield, 33% ee; the spectral data were comparable to those reported [53]. The ee was determined by HPLC analysis with Daicel Chiralcel OD-H (hexane/^{i}PrOH = 93/7, flow rate = 0.5 mL/min, t_r (minor) = 9.4 min, t_r (major) = 10.7 min). **4r**: 87% yield, 29% ee; the spectral data were comparable to those reported [53]. The ee was determined by HPLC analysis with Daicel Chiralcel OD-H (hexane/^{i}PrOH = 90/10, flow rate = 0.5 mL/min, t_r (minor) = 15.6 min, t_r (major) = 29.1 min).

4. Conclusions

The chiral 3,4,5,6-tetrahydropyrimidinium salts with bulky silyl groups were readily synthesized by a three-step method starting with commercial amino alcohols. In situ prepared corresponding carbenes, along with their parent carbenes, were then tested in an asymmetric diethylzinc addition of arylaldehydes, producing the product in good yield and better enantioselectivities. In brief, an example of improvement in performance of catalysts by modification of their OH group with a steric functional group has been shown. Further study of these tetrahydropyrimidinium salts as ligands for metal-mediated asymmetric catalysis are currently underway [54,55].

Supplementary Materials: The following are available online at http://www.mdpi.com/xxx/s1, Figure S1: ^{1}H and ^{13}C NMR Spectra of Compounds **2a**–**2i**, Table S1: Optimization of the reaction conditions.

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Author Contributions: Xiaoming Liu and Jie Li conceived and designed the experiments; Bihui Zhou and Yajie Jiang performed the experiments and analyzed the data; Xiaoming Liu and Jie Li wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Arduengo, A.J.; Harlow, R.L.; Kline, M.J. A stable crystalline carbene. *J. Am. Chem. Soc.* **1991**, *113*, 361–363. [CrossRef]
2. Herrmann, W.A.; Köcher, C. *N*-heterocyclic carbenes. *Angew. Chem. Int. Ed.* **1997**, *36*, 2162–2187. [CrossRef]
3. Bourissou, D.; Guerret, O.; Gabbaï, F.P.; Bertrand, G. Stable carbenes. *Chem. Rev.* **2000**, *100*, 39–92. [CrossRef] [PubMed]
4. Zinn, F.K.; Viciu, M.S.; Nolan, S.P. Carbenes: Reactivity and catalysis. *Annu. Rep. Prog. Chem. Sect. B Org. Chem.* **2004**, *100*, 231–249. [CrossRef]
5. Cavell, K.J.; McGuinness, D.S. Redox processes involving hydrocarbylmetal (*N*-heterocyclic carbene) complexes and associated imidazolium salts: Ramifications for catalysis. *Coord. Chem. Rev.* **2004**, *248*, 671–681. [CrossRef]
6. Peris, E.; Crabtree, R.H. Recent homogeneous catalytic applications of chelate and pincer *N*-heterocyclic carbenes. *Coord. Chem. Rev.* **2004**, *248*, 2239–2246. [CrossRef]
7. Crudden, C.M.; Allen, D.P. Stability and reactivity of *N*-heterocyclic carbene complexes. *Coord. Chem. Rev.* **2004**, *248*, 2247–2273. [CrossRef]
8. Pugh, D.; Danopoulos, A.A. Metal complexes with 'pincer'-type ligands incorporating *N*-heterocyclic carbene functionalities. *Coord. Chem. Rev.* **2007**, *251*, 610–641. [CrossRef]
9. Mata, J.A.; Poyatos, M.; Peris, E. Structural and catalytic properties of chelating bis- and tris-*N*-heterocyclic carbenes. *Coord. Chem. Rev.* **2007**, *251*, 841–859. [CrossRef]
10. Sommer, W.J.; Weck, M. Supported *N*-heterocyclic carbene complexes in catalysis. *Coord. Chem. Rev.* **2007**, *251*, 860–873. [CrossRef]
11. Hahn, F.E.; Jahnke, M.C. Heterocyclic carbenes: Synthesis and coordination chemistry. *Angew. Chem. Int. Ed.* **2008**, *47*, 3122–3172. [CrossRef] [PubMed]
12. Hopkinson, M.N.; Richter, C.; Schedler, M.; Glorius, F. An overview of *N*-heterocyclic carbenes. *Nature* **2014**, *510*, 485–496. [CrossRef] [PubMed]

13. Green, J.C.; Scur, R.G.; Arnold, P.L.; Cloke, G.N. An experimental and theoretical investigation of the electronic structure of Pd and Pt bis(carbene) complexes. *Chem. Commun.* **1997**, 1963–1964. [CrossRef]
14. Peris, E.; Loch, J.A.; Mata, J.; Crabtree, R.H. A Pd complex of a tridentate pincer CNC bis-carbene ligand as a robust homogenous Heck catalyst. *Chem. Commun.* **2001**, 201–202. [CrossRef]
15. Briot, A.; Bujard, M.; Gouverneur, V.; Nolan, S.P.; Mioskowski, C. Improvement in olefin metathesis using a new generation of ruthenium catalyst bearing an imidazolylidene ligand: Synthesis of heterocycles. *Org. Lett.* **2000**, *2*, 1517–1519. [CrossRef] [PubMed]
16. Perry, M.C.; Burgess, K. Chiral *N*-heterocyclic carbene-transition metal complexes in asymmetric catalysis. *Tetrahedron Asymmetry* **2003**, *14*, 951–961. [CrossRef]
17. César, V.; Bellemin-Laponnaz, S.; Gade, L.H. Chiral *N*-heterocyclic carbenes as stereodirecting ligands in asymmetric catalysis. *Chem. Soc. Rev.* **2004**, *33*, 619–636. [CrossRef] [PubMed]
18. Douthwaite, R.E. Metal-mediated asymmetric alkylation using chiral *N*-heterocyclic carbenes derived from chiral amines. *Coord. Chem. Rev.* **2007**, *251*, 702–717. [CrossRef]
19. Gade, L.H.; Bellemin-Laponnaz, S. Mixed oxazoline-carbenes as stereodirecting ligands for asymmetric catalysis. *Coord. Chem. Rev.* **2007**, *251*, 718–725. [CrossRef]
20. Snead, D.R.; Seo, H.; Hong, S. Recent developments of chiral diaminocarbene-metal complexes for asymmetric catalysis. *Curr. Org. Chem.* **2008**, *12*, 1370–1387. [CrossRef]
21. Wang, F.J.; Liu, L.J.; Wang, W.F.; Li, S.K.; Shi, M. Chiral NHC–metal-based asymmetric catalysis. *Coord. Chem. Rev.* **2012**, *256*, 804–853. [CrossRef]
22. Alder, R.W.; Blake, M.E.; Bortolotti, C.; Bufali, S.; Butts, C.P.; Linehan, E.; Oliva, J.M.; Orpen, A.G.; Quayle, M.J. Complexation of stable carbenes with alkali metals. *Chem. Commun.* **1999**, 241–242. [CrossRef]
23. Guillen, F.; Winn, C.L.; Alexakis, A. Enantioselective copper-catalyzed conjugate addition using chiral diaminocarbene ligands. *Tetrahedron Asymmetry* **2001**, *12*, 2083–2086. [CrossRef]
24. Bazinet, P.; Yap, G.P.A.; Richeson, D.S. Constructing a stable carbene with a novel topology and electronic framework. *J. Am. Chem. Soc.* **2003**, *125*, 13314–13315. [CrossRef] [PubMed]
25. Mayr, M.; Wurst, K.; Ongania, K.H.; Buchmeiser, M.R. 1,3-dialkyl- and 1,3-diaryl-3,4,5,6-tetrahydropyrimidin-2-ylidene rhodium(I) and palladium(II) complexes: Synthesis, structure, and reactivity. *Chem. Eur. J.* **2004**, *10*, 1256–1266. [CrossRef] [PubMed]
26. Herrmann, W.A.; Schneider, S.K.; Öfele, K.; Sakamoto, M.; Herdtweck, E. First silver complexes of tetrahydropyrimid-2-ylidenes. *J. Organomet. Chem.* **2004**, *689*, 2441–2449. [CrossRef]
27. Imlinger, N.; Mayr, M.; Wang, D.R.; Wurst, K.; Buchmeiser, M.R. Arylation of carbonyl compounds catalyzed by rhodium and iridium 1,3-R2-tetrahydropyrimidin-2-ylidenes: Structure-reactivity correlations. *Adv. Synth. Catal.* **2004**, *346*, 1836–1843. [CrossRef]
28. Yun, J.; Marinez, E.R.; Grubbs, R.H. A new ruthenium-based olefin metathesis catalyst coordinated with 1,3-dimesityl-1,4,5,6-tetrahydropyrimidin-2-ylidene: Synthesis, X-ray structure, and reactivity. *Organometallics* **2004**, *23*, 4172–4173. [CrossRef]
29. Yang, L.R.; Mayr, M.; Wurst, K.; Buchmeiser, M.R. Novel metathesis catalysts based on ruthenium 1,3-dimesityl-3,4,5,6-tetrahydropyrimidin-2-ylidenes: Synthesis, structure, immobilization, and catalytic activity. *Chem. Eur. J.* **2004**, *10*, 5761–5770. [CrossRef] [PubMed]
30. Bazinet, P.; Ong, T.G.; O'Brien, J.S.; Lavoie, N.; Bell, E.; Yap, G.P.A.; Korobkov, I.; Richeson, D.S. Design of sterically demanding, electron-rich carbene ligands with the perimidine scaffold. *Organometallics* **2007**, *26*, 2885–2895. [CrossRef]
31. Binobaid, A.; Iglesias, M.; Beetstra, D.J.; Kariuki, B.; Dervisi, A.; Fallis, I.A.; Cavell, K.J. Expanded ring and functionalised expanded ring *N*-heterocyclic carbenes as ligands in catalysis. *Dalton Trans.* **2009**, *35*, 7099–7112. [CrossRef] [PubMed]
32. Hill, A.F.; McQueen, C.M.A. Dihydroperimidine-derived *N*-heterocyclic pincer carbene complexes via double C–H activation. *Organometallics* **2012**, *31*, 8051–8054. [CrossRef]
33. Zhang, J.; Qin, X.K.; Fu, J.; Wang, X.; Su, X.L.; Hu, F.L.; Jiao, J.J.; Shi, M. Fine-tunable 3,4-dihydroquinazol-2-ylidene carbenes: Synthesis, rhodium(I) complexes, and reactivity. *Organometallics* **2012**, *31*, 8257–8282. [CrossRef]
34. Armstrong, R.; Ecott, C.; Ma Dunsford, J.J.; Tromp, D.S.; Cavell, K.J.; Elsevier, C.J.; Kariuki, B.M. *N*-alkyl functionalised expanded ring *N*-heterocyclic carbene complexes of rhodium(I) and iridium(I): Structural investigations and preliminary catalytic evaluation. *Dalton Trans.* **2013**, *42*, 7318–7329.

35. Yang, B.M.; Xiang, K.; Tu, Y.Q.; Zhang, S.H.; Yang, D.T.; Wang, S.H.; Zhang, M. Spiro-fused six-membered *N*-heterocyclic carbene: A new scaffold toward unique properties and activities. *Chem. Commun.* **2014**, *50*, 7163–7165. [CrossRef] [PubMed]
36. Verlinden, K.; Ganter, C. Converting a perimidine derivative to a cationic *N*-heterocyclic carbene. *J. Organomet. Chem.* **2014**, *750*, 23–29. [CrossRef]
37. Hill, A.F.; McQueen, C.M.A. Dihydroperimidine-derived PNP pincer complexes as intermediates en route to *N*-heterocyclic carbene pincer complexes. *Organometallics* **2014**, *33*, 1909–1912. [CrossRef]
38. Scarborough, C.C.; Grady, M.J.W.; Guzei, I.A.; Gandhi, B.A.; Bunel, E.E.; Stahl, S.S. Pd^{II} complexes possessing a seven-membered *N*-heterocyclic carbene ligand. *Angew. Chem. Int. Ed.* **2005**, *44*, 5269–5272. [CrossRef] [PubMed]
39. Scarborough, C.C.; Popp, B.V.; Guzei, I.A.; Stahl, S.S. Development of 7-membered *N*-heterocyclic carbene ligands for transition metals. *J. Organomet. Chem.* **2005**, *690*, 6143–6155. [CrossRef]
40. Rogers, M.M.; Wendlandt, J.E.; Guzei, I.A.; Stahl, S.S. Aerobic intramolecular oxidative amination of alkenes catalyzed by NHC-coordinated palladium complexes. *Org. Lett.* **2006**, *8*, 2257–2260. [CrossRef] [PubMed]
41. Iglesias, M.; Beetstra, D.J.; Stasch, A.; Horton, P.N.; Hursthouse, M.B.; Coles, S.J.; Cavell, K.J.; Dervisi, A.; Fallis, I.A. First examples of diazepanylidene carbenes and their late-transition-metal complexes. *Organometallics* **2007**, *26*, 4800–4809. [CrossRef]
42. Iglesias, M.; Beetstra, D.J.; Knight, J.C.; Ooi, L.L.; Stasch, A.; Coles, S.; Male, L.; Hursthouse, M.B.; Cavell, K.J.; Dervisi, A.; et al. Novel expanded ring *N*-heterocyclic carbenes: Free carbenes, silver complexes, and structures. *Organometallics* **2008**, *27*, 3279–3289. [CrossRef]
43. Scarborough, C.C.; Guzei, I.A.; Stahl, S.S. Synthesis and isolation of a stable, axially-chiral seven-membered *N*-heterocyclic carbene. *Dalton Trans.* **2009**, *13*, 2284–2286. [CrossRef] [PubMed]
44. Iglesias, M.; Beetstra, D.J.; Kariuki, B.; Cavell, K.J.; Dervisi, A.; Fallis, I.A. Synthesis and structural features of rhodium complexes of expanded ring *N*-heterocyclic carbenes. *Eur. J. Inorg. Chem.* **2009**, 1913–1919. [CrossRef]
45. Newman, P.D.; Cavell, K.J.; Kariuki, B. Metal complexes of chiral NHCs containing a fused six- and seven-membered central ring. *Organometallics* **2010**, *29*, 2724–2734. [CrossRef]
46. Hudnall, T.W.; Tennyson, A.G.; Bielawski, C.W. A seven-membered *N*, *N*′-diamidocarbene. *Organometallics* **2010**, *29*, 4569–4578. [CrossRef]
47. Dunsford, J.J.; Cavell, K.J.; Kariuki, B.M. Gold(I) complexes bearing sterically imposing, saturated six- and seven-membered expanded ring *N*heterocyclic carbene ligands. *Organometallics* **2012**, *31*, 4118–4121. [CrossRef]
48. Hauwert, P.; Dunford, J.J.; Tromp, D.S.; Weigand, J.J.; Lutz, M.; Cavell, K.J.; Elsevier, C.J. Zerovalent [Pd(NHC)(Alkene)1,2] complexes bearing expanded-ring *N*-heterocyclic carbene ligands in transfer hydrogenation of alkynes. *Organometallics* **2013**, *32*, 131–140. [CrossRef]
49. Dunsford, J.J.; Cavell, K.J. Pd–PEPPSI-type expanded ring *N*-heterocyclic carbene complexes: Synthesis, characterization, and catalytic activity in Suzuki–Miyaura cross coupling. *Organometallics* **2014**, *33*, 2902–2905. [CrossRef]
50. Li, J.; Shen, W.X.; Li, X.R. Recent developments of expanded ring *N*-heterocyclic carbenes. *Curr. Org. Chem.* **2012**, *16*, 2879–2891. [CrossRef]
51. Li, J.; Xu, L. Novel C_2-symmetric six-membered NHCs for asymmetric copper-catalysed conjugate addition of Grignard reagents to 3-methylhexenone. *Tetrahedron* **2015**, *71*, 2858–2862. [CrossRef]
52. Zhou, B.H.; Wu, C.; Chen, X.X.; Huang, H.X.; Li, L.L.; Fan, L.M.; Li, J. New C_2-symmetric six-membered carbine ligands incorporating two hydroxyl groups for palladium-catalyzed deprotonative-cross-coupling processes (DCCP) of sp^3 C–H bonds in diarylmethanes. *Tetrahedron Lett.* **2017**, *58*, 4157–4161. [CrossRef]
53. Zhou, B.H.; He, W.P.; Li, L.L.; Fan, L.M.; Li, X.R.; Li, J. Synthesis of novel chiral pyrimidone salts and their application in asymmetric diethylzinc addition of arylaldehydes. *Curr. Org. Synth.* **2017**, *14*. [CrossRef]

54. Nitti, A.; Bianchi, G.; Po, R.; Swager, T.M.; Pasini, D. Domino direct arylation and cross-aldol for rapid construction of extended polycyclic π-scaffolds. *J. Am. Chem. Soc.* **2017**, *139*, 8788–8791. [CrossRef] [PubMed]
55. Nitti, A.; Signorile, M.; Boiocchi, M.; Bianchi, G.; Po, R.; Pasini, D. Conjugated thiophene-fused isatin dyes through intramolecular direct arylation. *J. Org. Chem.* **2016**, *81*, 11035–11042. [CrossRef] [PubMed]