Tetrahedron Letters 69 (2021) 152974

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Regio- and stereoselective synthesis of cyclobutanes by nickel-catalyzed homodimerizative [2 + 2] cycloaddition using allenamides

Yuna Kawata [a], Shigeru Arai [a,b,*], Masaya Nakajima [a], Atsushi Nishida [a]

[a] Graduate School of Pharmaceutical Sciences, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba 260-8675, Japan
[b] Molecular Chirality Research Center, Chiba University, 1-33, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

ARTICLE INFO

Article history:
Received 7 February 2021
Revised 26 February 2021
Accepted 1 March 2021
Available online 9 March 2021

Keywords:
Nickel
Cycloaddition
Allenamides
DFT study
Homodimerization

ABSTRACT

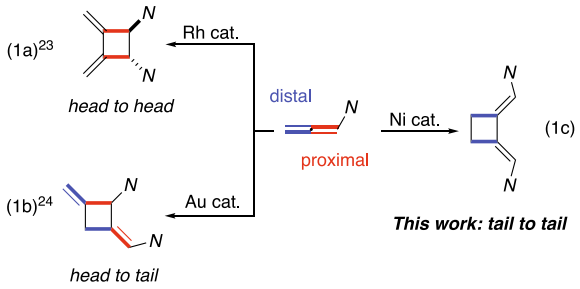
Highly regio- and stereoselective homodimerizative [2 + 2] cycloaddition of allenamides under nickel catalysis was developed. Xantphos is an essential ligand to give "*tail to tail*" products and DFT studies revealed that oxidative addition between a nickel(0) complex and two distal C=C bonds of the allenamides would be a key process. Sequential formation of the metallacycle intermediate would proceed in both a regio- and stereoselective manner to give the corresponding cyclobutane as a single isomer.

Introduction

Cyclobutanes are important structural motifs for biologically important compounds and natural products [1,2]. Their efficient synthesis has been a major topic in synthetic organic chemistry and one of the most reliable strategies for obtaining them has been the [2 + 2] cycloaddition reaction [3–5]. In particular, the use of allenes (C=C=C) as *C*2 components has been attractive because of their higher reactivity compared to simple olefins and the synthetic utility of the products involving additional C=C bonds [6–13]. To enhance the synthetic utility of allenes, the use of allenamides (*N*-C=C=C) has been option to give nitrogen-functionalized cyclobutanes [14,15], and various metal species [16] including gold complexes [17–22] have been shown to be effective catalysts for heterodimerizative [2 + 2] cycloaddition.

On the other hand, the catalytic applications of a homodimerizative strategy for [2 + 2] cycloaddition using allenamides have been limited to only 2 modes of cycloaddition (Scheme 1). One of these is rhodium catalysis, which connects two proximal bonds (red) to give "*head to head*" *trans*-cycloadducts (Eq. (1a)) [23], whereas gold catalysis promotes "*head to tail*" dimerization (eq. 1b) [24]. An alternative synthetic method to an as yet unknown carbon skeleton would be highly desirable and we herein describe a new application of "*tail to tail*" homodimerization (eq. 1c). The choice of xantphos is essential to achieve higher selectivity and efficacy, which could be reasonably explained by DFT studies. These suggest that the initial metallacycle formation would determine both the regio- and stereoselectivity of the products. This unprecedented "*tail to tail*" mode of cycloaddition through homodimerization of allenamides would also provide a new synthetic option in metal catalysis, since Saito and co-workers have used the simple allenes for the nickel-catalyzed [2 + 2] cycloaddition reaction [25].

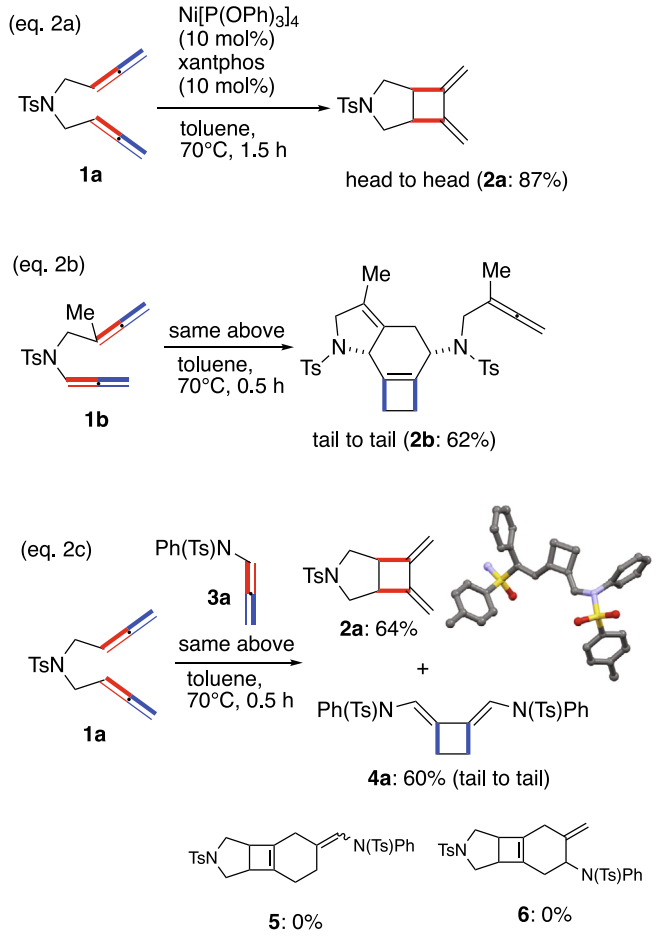
Our previous and preliminary studies on nickel- catalyzed [2 + 2] cycloaddition effectively discriminated C=C bonds in allenes and allenamides (Scheme 2). For example, bisallene (**1a**) smoothly underwent an intramolecular reaction to give "*head to*



Scheme 1. Metal-Catalyzed Homodimerizative [2 + 2] Cycloaddition of Allenamides.

* Corresponding author.
E-mail address: araisgr@chiba-u.jp (S. Arai).

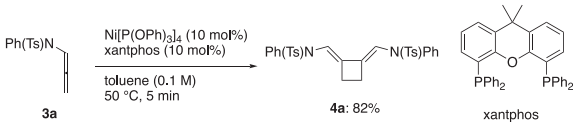
https://doi.org/10.1016/j.tetlet.2021.152974
0040-4039/



Scheme 2. Reactivity of Allenes and Allenamides under Nickel-Catalyzed [2 + 2] Cycloaddition.

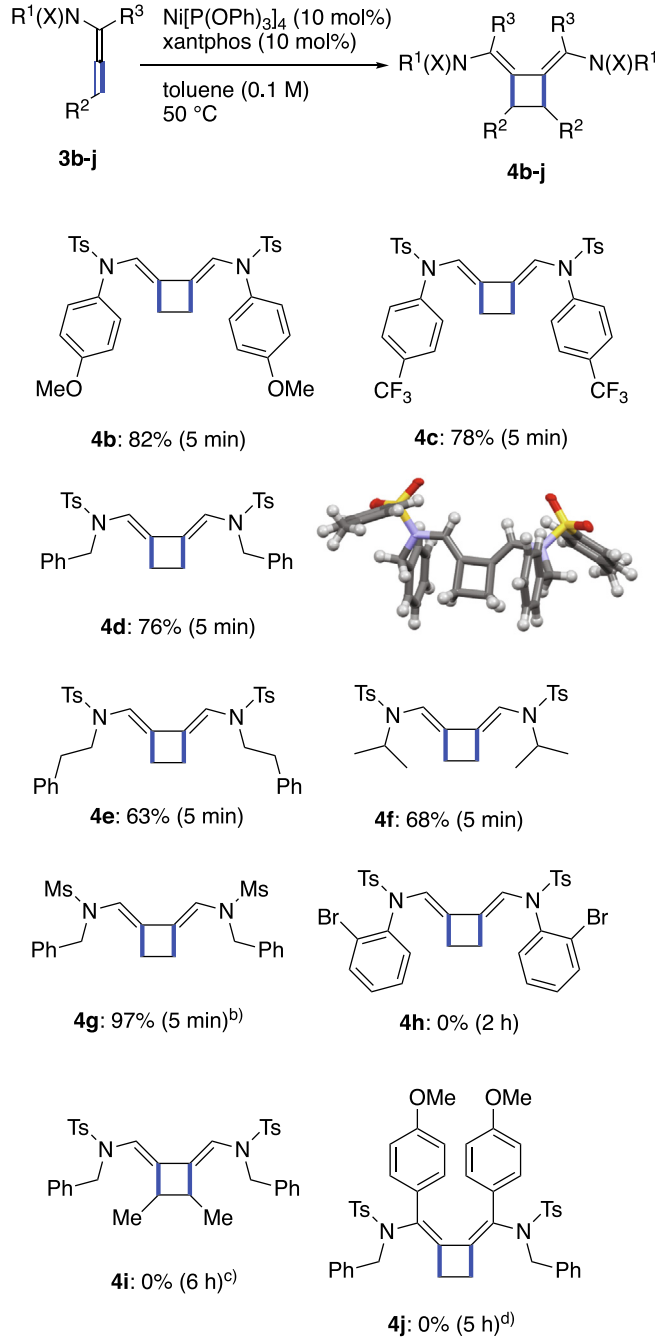
head" products (**2a**) exclusively (eq. 2a) [26,27], whereas the allene-allenamide (**1b**) promoted a [2 + 2]/[4 + 2] cycloaddition sequence to give a single "*tail to tail*" product (**2b**). Its structure indicates that the distal bond of allenamides favorably dimerized to the cyclobutene, regioselectively (Eq. (2b)) [26]. When a mixture of **1a** and **3a** was subjected to similar conditions, **2a** and **4a** were isolated in respective yields of 64% and 60% without any further cycloaddition products such as **5** and **6** (eq. 2c). The regio- and stereochemistry of **4a** was confirmed to be (*E*,*E*) by X-ray crystallographic analysis [28]. These results prompted us to better understand the behavior and reactivity of **3a** and to continue further investigations for the establishment of a new catalysis.

Table 1
Optimization of reaction conditions.



Entry	Change from standard conditions	Yield of **4a** %[a]	Recov. of **3a** %
1	70 °C, 5 min	75	0
2	rt, 16 h	7	87
3	No xantphos, 70 °C, 30 min	2	0
4	PPh_3 (20 mol%), 50 °C, 5 min	44	3
5	dppb (10 mol%), 50 °C, 5 min	14	9
6	CH_2Cl_2, 50 °C, 5 min	81	0
7	THF, 50 °C, 5 min	67	0
8	No nickel catalyst, 50 °C, 30 min	0	90
9	No nickel catalyst,, no xantphos, 50 °C, 30 min	0	92
10	$P(OPh)_3$ (40 mol%) instead of nickel catalyst, 50 °C, 30 min	0	46
11	$NiCl_2$ (10 mol%) with xantphos (10 mol%), 50 °C, 30 min	0	98

[a] Chemical yields of **4a** were determined by ^{1}H NMR analysis using Ph_3CH as an internal standard.



a) The yield of **4b-g** are determined by ^{1}H NMR analysis using PH_3CH as an internal standard.
b) 95% purity of substrate was used.
c) **3i** was recovered in 93% yield.
d) **3j** was recovered in 87% yield.

Scheme 3. Substrate Scope for Homodimerizative [2 + 2] Cycloaddition using **3b-j**[a].

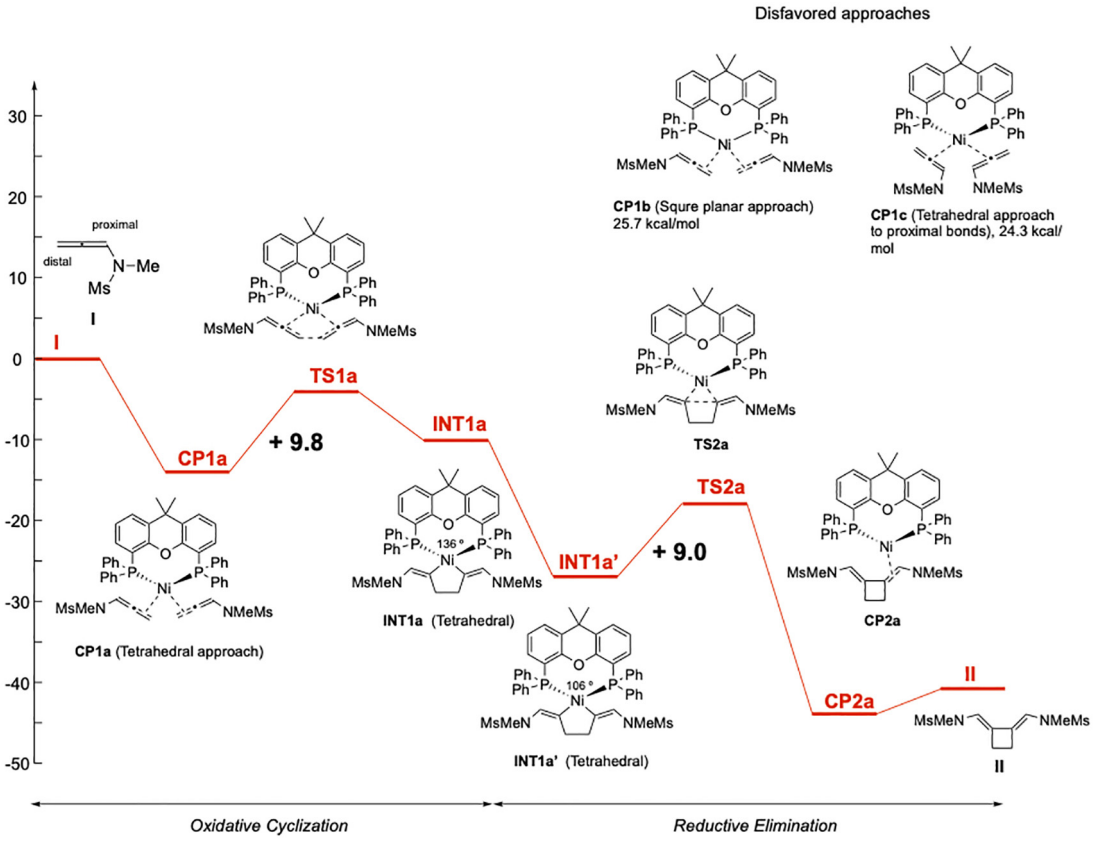


Fig. 1. Energy Diagram for Ni-Catalyzed Homodimerizative [2 + 2] Cycloaddition.

We initiated our studies by investigating the cycloaddition of **3a** under standard conditions [$Ni[P(OPh)_3]_4$ (10 mol%), xantphos (10 mol%), toluene, 50 °C). The reaction went to completion in 5 min to give **4a** in 82% yield without any regio- or stereoisomeric products. Higher temperature (70 °C) was also effective to complete the reaction in 5 min, however the yield of **4a** was slightly decreased (entry 1). A room temperature condition was ineffective and gave **4a** in only 4% yield and **3a** was recovered in 87% yield even after 16 h (entry 2). The absence of xantphos prevented both the conversion to **4a** and the recovery of **3a**, and unidentified products were observed (entry 3). Other phosphines such as PPh_3 and 1,4-diphenylphosphinobutane (dppb) gave lower conversion to **4a** during the decomposition of **3a** (entries 4 and 5). The use of dichloromethane and THF as solvents at 50 °C gave the exclusive formation of **4a** in respective yields of 81% and 67% (entries 6 and 7). This reaction did not proceed without nickel(0) species with/without xantphos (entries 8 and 9). The eliminated phosphite would not give any influence because the reaction using $P(OPh)_3$ (40 mol%) did not work act as a promotor at all (entry 10). Finally, a catalytic amount of $NiCl_2$ instead of Ni(0) also gave the recovery of **3a**. The results summarized in Table 1 show the Ni(0)-xantphos is an essential combination to promote the [2 + 2] cycloaddition reaction of **3a**.

The optimum condition (toluene, 50 °C) were next applied with various substrates (Scheme 3). The electronic effect of the para substituents in **3b** and **3c** did not influence the reaction efficacy and gave the corresponding products **4b** and **4c** in respective yields of 82% and 78%. *N*-Alkyl groups instead of aryl groups were also effective for a smooth cycloaddition reaction; for example, *N*-Benzyl substrate gave **4d** in 76% yield. Substrates bearing phenethyl and isopropyl groups were both quickly transformed to give **4e** and **4f** in respective yields of 63% and 68%. Finally, a methanesulfonyl group on nitrogen was investigated to give **4 g** in 97% yield. In all cases, the reaction proceeded to exclusively give the corresponding cycloadducts as a single isomer. A reactive moiety of the aromatic bromide bond in **3h** was unsuitable due to its reactivity toward Ni(0) species and the messy reaction gave no cycloadducts. The substituents around the allenyl double bonds in **3** gave a serious decrease in reactivity; for example, a methyl group (R^2) in **3i** and an aryl group in **3j** both prevented cycloaddition and the expected adducts were not obtained at all even after 5 h. This would be because the steric bulk of substituents would be unsuitable for interacting with a nickel complex and the reaction resulted in recovery of the starting allenamides in respective yields of 93% and 87%.

To obtain insights into the mechanism of this catalytic transformation, we performed density functional theory (DFT) calculations (M06/LANL2DZ/6-31G*) with **I** as a model substrate (Fig. 1). These DFT studies suggested that the reaction is initiated by the formation of **CP1a**. The key feature for promotion of C—C bond formation is tetrahedral approach by a Ni(0)-xantphos complex [29], and the metallacycle formation would be help to overcome the activation energy through **TS1a** (9.8 kcal/mol). Other possible transition-state models such as **TS1b** and **TS1c** would be unlikely to form the corresponding metallacycles because of their higher activation energies of 25.7 kcal/mol and 24.3 kcal/mol, respectively (see the Supporting Information). After distortion of the P-Ni-P angle is released to **INT1a'** (from 136° to 106°), the subsequent reductive elimination step to **TS2a** requires 9.0 kcal/mol, which could be accelerated by the larger bite angle of xantphos [30]. Finally, the dissociation of **II** from **CP2a** generates a Ni-xantphos complex to promote catalytic turnover. The tetrahedral nickel center in both **TS1a** and **TS2a** could minimize the steric repulsion between PPh_2 and N(Ms)Me groups, and their activation energies (less than

10 kcal/mol) are much smaller than those of the reverse processes (more than 20 kcal/mol for both **CP2a** → **TS2a** and **INT1a'**→**TS1a**). This could explain the irreversibility to complete the reaction within 5 min.

Conclusions

In conclusion, we have developed an efficient nickel-catalyzed [2 + 2] cycloaddition using allenamides. Xantphos was found to be essential ligand for the reaction efficacy and the most operative mechanism could be supported by DFT calculations. Further investigations aimed at synthetic applications to the fused ring system and complex molecules using this methodology are currently underway in our laboratory.

Experimental section

*General procedure for Ni-catalyzed homodimerizative [2 + 2] cycloaddition of **3a***

To a solution of **3a** (51.4 mg, 0.18 mmol) in toluene (1.8 mL, 0.1 M) was added $Ni[P(OPh)_3]_4$ (23.5 mg, 0.018 mmol, 10 mol%) and xantphos (10.4 mg, 0.018 mmol, 10 mol%), and the reaction mixture was heated at 50 °C for 5 min under argon atmosphere. After the reaction mixture was cooled to room temperature, it was filtered through a Celite pad. Removal of the solvent under vacuum gave a mixture of the product, which was estimated to be 42.1 mg of **4a** (82%) by ^1H NMR analysis using Ph_3CH as an internal standard.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by the Grant-in-Aid from the Japan Society for the Promotion of Science (JSPS) (Grant No. 17K08205).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.152974.

References

[1] V.M. Dembitsky, J. Nat. Med. 62 (2008) 1–33.
[2] S. Yu, S. Ma, Angew. Chem. Int. Ed. 51 (2012) 3074–3112.
[3] S. Ma, Chem. Rev. 105 (2005) 2829–2871.
[4] C. Aubert, L. Fensterbank, P. Garcia, M. Malacria, A. Simonneau, Chem. Rev. 111 (2011) 1954–1993.
[5] J.L. Mascareñas, I. Varela, F. Lopéz, Acc. Chem. Res. 52 (2019) 465–479.
[6] M. Gulias, A. Collado, B. Trillo, F. López, E. Oñate, M.A. Esteruelas, J.L. Mascareñas, Recent catalytic applications of [2+2] cycloadditions using simple allenes Au, J. Am. Chem. Soc. 133 (2011) 7660–7663.
[7] M.R. Luzung, P. Mauleón, F.D. Toste, J. Am. Chem. Soc. 129 (2007) 12402–12403.
[8] M.L. Conner, M.K. Brown, J. Org. Chem. 81 (2016) 8050–8060.
[9] Y. Xu, Y.J. Hong, D.J. Tantillo, M.K. Brown, Org. Lett. 19 (2017) 3703–3706.
[10] J.M. Wiest, M.L. Conner, M.K. Brown, J. Am. Chem. Soc. 140 (2018) 15943–15949.
[11] E.M. Hancock, E.L. Kuker, D.J. Tantillo, M.K. Brown, Angew. Chem. Int. Ed. 59 (2020) 436–441.
[12] T.L.N. Nguyen, C.A. Incerti-Pradillos, W. Lewis, H.W. Lam, Chem. Commun. 54 (2018) 5622–5625.
[13] N.N. Noucti, E.J. Alexanian, Angew. Chem. Int. Ed. 54 (2015) 5447–5450.
[14] E. Manoni, M. Bandini, Eur. J. Org. Chem. (2016) 3135–3142.
[15] T. Liu, Z. Lu, Z.-X. Ma, Y. Zhang, R.P. Hsung, Chem. Rev. 113 (2013) 4862–4904.
[16] (a) M. He, N. Chen, T. Zhou, Q. Li, H. Li, M. Lang, J. Wang, S. Peng, Org. Lett. 21 (2019) 9559–9563. (b) X. Zhong, Q. Tang, P. Zhou, Z. Zhong, S. Dong, X. Liu, X. Feng, Chem. Commun. 54 (2018) 10511–10514. (c) R.-R. Liu, J.-P. Hu, J.-J. Hong, C.-J. Lu, J.-R, Gao, Y.-X. Jia, Chem. Sci. 8 (2017) 2811–2815.
[17] R. Ocello, A.D. Nisi, M. Jia, Q.-Q. Yang, M. Monari, P. Giacinto, A. Bottoni, G.P. Miscione, M. Bandini, Chem. Eur. J. 21 (2015) 18445–18453.
[18] H. Faustino, P. Bernal, L. Castedo, F. Lopéz, J.L. Mascareñas, Adv. Synth. Catal. 354 (2012) 1658–1664.
[19] M. Jia, M. Monari, Q.-Q. Yang, M. Bandini, Chem. Commun. 51, 2320–2323.
[20] S. Suárez-Pantiga, C. Hernández-Díaz, E. Rubio, J.M. González, Angew. Chem. Int. Ed. 51 (2012) 11552–11555.
[21] S. Suárez-Pantiga, C. Hernández-Díaz, M. Piedrafita, E. Rubio, J.M. González, Adv. Synth. Catal. 354 (2012) 1651–1657.
[22] H. Hu, Y. Wang, D. Qian, Z.-M. Zhang, L. Liu, J. Zhang, Org. Chem. Front. 3 (2016) 759–763.
[23] (a) W.-H. Zheng, P. P. Bora, G.-J. Sun, Q. Kang, Org. Lett. 18 (2016) 3694–3697. (b) W.-F. Zheng, G.-J. Sun, L. Chen, Q. Kang, Adv. Synth. Catal. 360 (2018) 1790–1794.
[24] (a) X.-X. Li, L.-L. Zhu, Z. Chen, Org. Lett. 14 (2012) 436–439. (b) S. Yu, J. Chen, G. Liu, J. Lei, W. Hu, H. Qiu, Chem. Commun. 56 (2020) 1649–1652.
[25] S. Saito, K. Hirayama, C. Kabuto, Y. Yamamoto, J. Am. Chem. Soc. 122 (2000) 10776–10780. (b) E. Bustelo, C. Gueroy, A. Hercouet, B. Carboni, L. Toupet, P.H. Dixneuf, J. Am. Chem. Soc. 127 (2005) 11582–11583.
[26] S. Arai, Y. Kawata, Y. Amako, A. Nishida, Tetrahedron Lett. 60 (2019) 151168.
[27] X. Jian, X. Cheng, S. Ma, Angew. Chem. Int. Ed. 45 (2006) 8009–8013.
[28] The supplementary crystallographic data for this paper can be found at CCDC 2057133 (**4a**) and 2060060 (**4d**).
[29] (a) P. Kumar, S. Prescher, J. Louie, Angew. Chem. Int. Ed. 50 (2011) 10694–10698. (b) W.G. Kim, M.E. Kang, J.B. Lee, M.H. Jeon, S. Lee, J. Lee, B. Choi, P. M.S. D. Cal, S. Kang, J.-M. Kee, G.J.L. Bernardes, J.-U. Rohde, W. Choe, S.Y. Hong, J. Am. Chem. Soc. 139 (2017) 12121–12124.
[30] P.W.N.M. van Leeuwen, P.C.J. Kamer, J.N.H. Reek, P. Dierkes, Chem. Rev. 100 (2000) 2741–2769.