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Carbene-Catalyzed Enantioselective Aromatic N-Nucleophilic Addition of Heteroarenes to Ketones

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Abstract: The aromatic nitrogen atoms of heteroarylaldehydes are activated by carbene catalysts to react with ketone electrophiles. Multi-functionalized cyclic N,O-acetal products are afforded in good to excellent yields and optical purities. Our reaction involves the formation of an unprecedented aza-fulvene-type acylazolium intermediate. A broad range of N-heteroaromatic aldehydes and electron-deficient ketone substrates works effectively in this transformation. Several of the chiral N,O-acetal products afforded through this protocol exhibit excellent antibacterial activities against *Ralstonia solanacearum* (Rs) and are valuable in the development of novel agrichemicals for plant protection.

Introduction

Heteroarenes are privileged structures with a large presence in medicines, pesticides, ligands, natural products, and other functional molecules. The heteroatoms in some of these aryl molecules, such as indoles and pyrroles, can serve as convenient handles for structural modifications and alternations of functionality. For example, the nitrogen atoms of indole molecules can undergo addition reactions with reactive ketones to form N,O-acetals.^[1,2] Acetals are versatile structural motifs with applications in organic synthesis^[3,4] and pharmaceutical research.^[5–9] Most acetal-forming reactions can be made very efficient. The main challenges, however, lies on controlling the enantioselectivities of these transformations. In the field of transition-metal-free catalysis, chiral phosphoric-acid catalysts have found impressive success in

the mediation of asymmetric acetal formations, as pioneered by Antilla,^[10] List,^[11] and others.^[12,13]

We are interested in exploring N-heterocyclic carbenes (NHCs) as key organic catalysts for new activations and enantioselective reactions. In the past, NHCs were mostly used to activate carbon atoms (Scheme 1 a).^[14–26] The carbon atoms were activated as either nucleophilic or electrophilic reactive centers. In 2017, Chi and co-workers found that through the addition of a carbene to the aldehyde moiety of a 2-hydroxyl benzaldehyde under oxidative conditions, the phenol oxygen atom could be activated for enantioselective reactions.^[27] This activation converted the acylazolium to an *ortho*-quinone methide (*o*-QM) intermediate with the oxygen as the reactive center (Scheme 1 b, left). Very recently, Scheidt and co-workers disclosed that *N*-methylisatoic anhydrides could serve as N-centered nucleophile precursors under the catalysis of NHCs and gave aza-*o*-QM intermediates to react with electrophilic ketone substrates (Scheme 1 b, right).^[28]

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Scheme 1. NHC-promoted carbon and heteroatom activations.

In both the studies of Chi and Scheidt, the heteroatoms are not part of the p-system of the aryl rings. To the best of our knowledge, a carbene-catalyzed activation of heteroatoms that are part of the aromatic p-rings for asymmetric reactions has not been developed. In a broader picture, it remains difficult to push the use of carbene catalysts towards aromatic molecules.^[29–33]

Here we disclose that the NH units of indoles and pyrroles can be activated via carbene catalysis for enantioselective additions to reactive ketones (Scheme 1 c). The reaction starts with the addition of a carbene catalyst to the aldehyde moiety attached to indoles or pyrroles. Under oxidative conditions, this carbene-addition reaction forms acylazolium intermediate I. This oxidative process removes electron density from the indole (or pyrrole) and makes the overall p-system less nucleophilic compared to the arylaldehyde substrate. For instance, as a potential nucleophilic center, the carbon in 2- or 3-position^[34–36] is deactivated through the formation of I. On the contrary, the nitrogen atom^[37,38] is selectively activated as a reactive center through deprotonation of I to form the aza-

fulvene intermediate II.^[39–43] An enantioselective aza-nucleophilic addition of II to a ketone substrate followed by intramolecular ester formation provides the final acetal products with excellent yields and *er* values. Both indole and pyrrole aldehydes are effective substrates, and multiple types of ketones can serve as electrophiles.^[44] It is worth noting that Jørgensen and co-workers have recently disclosed the enantioselective N-functionalization of heteroaromatic aldehydes with chiral secondary amines used as the key organic catalysts.^[45]

Results and Discussion

We first chose indole aldehyde 1a and isatin 2a as model substrates in the presence of the DQ oxidant^[46] to search for suitable conditions. Selected results are provided in Table 1. NHC catalysts derived from aminoindanol skeletons were evaluated for this transformation (Table 1, entries 1–5). NHC pre-catalyst A^[47,48] bearing an *N*-Mes substituent can promote the formation of the desired product 3a in a moderate yield and excellent enantioselectivity (entry 1). No desired product could be observed when using NHC pre-catalyst B^[49] (entry 2). Although the use of NHC pre-catalyst C^[49] bearing an *N*-C₆F₅ substituent could give product 3a in nearly quantitative yield, the enantioselectivity was poor (entry 3). Both the product yield and *er* value could be increased with the use of pre-catalyst D^[50] (entry 4). The yield of 3a could be further improved by switching the anion of pre-catalyst D from BF₄[−] to Cl[−] (to form pre-catalyst E) without a decline of the reaction enantioselectivity (entry 5). Both organic and inorganic bases with mild basicities could be used in this reaction, and the desired product 3a formed in good to excellent yields and *er* values (entries 6 and 7). The use of strong bases (such as DBU) resulted in the decomposition of the *N,O*-acetal product 3a, thus leading to poor yields (entry 8). Multiple solvents were studied (entries 9–11). In general, solvents other than THF did not perform well (see Supporting Information): either yields or *er* values were

Table 1: Condition optimization for the aza-[3+2] cycloaddition reaction between indole aldehyde 1a and isatin 2a.^[a]

Entry	NHC	base	solvent	yield [%] ^[b]	<i>er</i> ^[c]
1	A	Et ₃ N	THF	58	94:6
2	B	Et ₃ N	THF	0	–
3	C	Et ₃ N	THF	99	59:41
4	D	Et ₃ N	THF	74	94:6
5	E	Et ₃ N	THF	99	94:6
6	E	DIEA	THF	99	95:5
7	E	NaOAc	THF	84	95:5
8	E	DBU	THF	28	54:46
9	E	DIEA	Toluene	79	95:5
10	E	DIEA	MTBE	49	96:4
11	E	DIEA	CH ₃ CN	59	60:40
12	E	DIEA	THF	99 (88)	96:4

[a] General conditions: 1a (0.15 mmol), 2a (0.10 mmol), NHC (0.02 mmol), base (0.17 mmol), DQ (0.17 mmol), solvent (1.0 mL), rt, 24 h. [b] The yields of 3a were determined via ¹H NMR with *sym*-trimethoxybenzene used as the internal standard. The data in the parentheses indicates the isolated yield of 3a after purification by column chromatography. [c] The *er* was determined via HPLC on a chiral stationary phase. [d] 1a (0.15 mmol), 2a (0.10 mmol), E (0.005 mmol), DIEA (0.15 mmol), DQ (0.17 mmol), THF (1.0 mL), 108°C, 24 h.

significantly decreased, likely due to partial decomposition and reversible reaction of the acetal products (entry 11). To our delight, the enantioselectivity could be further improved when carrying out the reaction with 5 mol % of NHC catalyst E at 108°C, where the excellent yield of 3a was retained (entry 12). On a technical note, the *N,O*-acetal product 3a exhibited good stability under these conditions and the reaction also showed tolerance to slight condition variations.^[51,52]

Having identified acceptable conditions for this enantioselective aza-[3+2] cycloaddition reaction, we examined the scope of both indole aldehydes (1) and isatins (2) (Figure 1). Substituents possessing both electron-donating and electron-withdrawing properties could be attached at each position of the benzene rings of the indole aldehydes (1), with the corresponding products (3) afforded in good to excellent yields and enantioselectivities (Figure 1, 3b–l). Various substituents were also tolerated on the isatin substrates (2), regardless of their electronic properties or substitution patterns (4a–v). The reaction also proceeded smoothly with the isatin bearing an *N*-methyl group without much decline of the product *er* value (4w). A more sterically hindered *N*-Trt protecting group led to product 4x with excellent optical purity, albeit also a lower yield under the current standard conditions.

Figure 1. Scope of indole aldehydes **1** and isatins **2**. General conditions: **1** (0.15 mmol), **2** (0.10 mmol), **E** (0.005 mmol), DIEA (0.15 mmol), DQ (0.17 mmol), THF (1.0 mL), 108°C, 24 h. [a] The reaction was carried out at a 1.0 mmol scale based on **2a**.

This aza-[3+2] cycloaddition reaction of indole aldehydes (**1**) can be considered a general approach for the asymmetric synthesis of various *N,O*-acetal indoline products (Figure 2). Electron-deficient ketoesters (**5**) are another class of suitable electrophiles for this NHC-catalyzed process. After a quick re-evaluation of the reaction conditions, the cyclic *N,O*-acetal products **6** could be afforded in good to excellent yields and enantioselectivities. One acceptable condition involves the use of pre-catalyst **C** (20 mol %) as the reaction catalyst, DIEA (250 mol %) as the base, and MTBE as the reaction solvent in the presence of the DQ oxidant (250 mol %). Specifically, indole aldehydes (**1**) bearing various substituents

or substitution patterns could react effectively (**6a–g**). Both electron-withdrawing and electron-donating substituents could be attached at the 3- or 4-positions of the benzene rings of the ketoester substrates (**6h** to **6k**). Interestingly, although the 2-FC₆H₄-substituted ketoester substrate worked well in this transformation (**6l**), 2-Cl and 2-Br substituents on the benzene rings of the ketoester substrates gave the desired products **6m** and **6n** in lower enantioselectivities. This is probably due to the higher steric hindrance between the two reaction substrates during the catalytic process. A variety of ester groups was also tolerated on the ketoester substrates (**6o** to **6r**), albeit only poor *er* values were obtained with

Figure 2. Scope of indole aldehydes 1 and ketones 5. General conditions: 1 (0.25 mmol), 5 (0.10 mmol), E (0.02 mmol), DIEA (0.25 mmol), DQ (0.25 mmol), MTBE (1.0 mL), 45°C, 24 h. [a] The reaction was carried out at a 1.0 mmol scale based on 5a.

benzhydrol (6 q) and phenol (6 r) esters. Replacement of the ester group on the ketoester substrate with either an amide group or a phosphoric ester group resulted in no or trace formation of the desired *N,O*-acetal products (6s or 6 t).

To further demonstrate the generality and utility of this NHC-catalyzed nitrogen-atom-activation approach, we investigated pyrrole aldehyde 7a (Table 2) as the heteroarene substrate next. The earlier conditions used for indole aldehydes (Figures 1 and 2) did not work well here, so we searched for a new set of conditions for the activation and reaction of pyrrole aldehydes. To our delight, the aza-[3+2] cycloaddition reaction between pyrrole aldehyde 7a and *N*-Bn isatin 2a proceeded smoothly using NHC pre-catalyst A or C, although the products 9 a' could only be afforded with very poor enantioselectivities (Table 2, entries 1 and 3). NHC pre-catalyst B bearing an *N*-Ph substituent was not effective for this process (entry 2). The enantioselectivity of the aza-[3+2] cycloaddition reaction could be dramatically improved by using *N*-Trt isatin 8a as the reaction substrate, with the corresponding product 9a afforded in 86:14 *er* (entry 4). Lewis acids have been shown to be promising co-catalysts that can enhance stereoselective control in multiple NHC-catalytic reactions.^[24,53] We therefore examined Lewis acids as ω -catalysts (entries 5–7) and found that the addition of urea molecule G^[27] could successfully enhance the reaction *er* from 86:14 (entry 4) to 90:10 (entry 7). Organic or inorganic bases with strong basicities resulted in a decomposition of the *N,O*-acetal products (entry 8). KOAc performed better than K₂CO₃ (entries 9 and 7, respectively). A survey of solvents revealed that CHCl₃ was the most suitable choice (entry 10). An acceptable condition was eventually found as using

10 mol % of NHC pre-catalyst C with 130 mol % of KOAc, 10 mol % of urea G in CHCl₃ at 0 °C in the presence of 120 mol % of the DQ oxidant (entry 11).

Table 2: Condition optimization for the aza-[3+2] cycloaddition reaction between pyrrole aldehyde 7a and isatin 2a or 8a.^[a]

Entry	ketone	NHC	additive	base	solvent	yield [%] ^[b] <i>er</i> ^[c]
1	2a	A		K ₂ CO ₃	CH ₂ Cl ₂	36 58:42
2	2a	B		K ₂ CO ₃	CH ₂ Cl ₂	0 –
3	2a	C		K ₂ CO ₃	CH ₂ Cl ₂	42 60:40
4	8a	C		K ₂ CO ₃	CH ₂ Cl ₂	30 86:14
5	8a	C	Sc(OTf) ₃	K ₂ CO ₃	CH ₂ Cl ₂	31 85:15
6	8a	C	F	K ₂ CO ₃	CH ₂ Cl ₂	40 87:13
7	8a	C	G	K ₂ CO ₃	CH ₂ Cl ₂	34 90:10
8	8a	C	G	Cs ₂ CO ₃ /DBU	CH ₂ Cl ₂	0 –
9	8a	C	G	KOAc	CH ₂ Cl ₂	47 90:10
10	8a	C	G	KOAc	CHCl ₃	88 93:7
11 ^[d]	8a	C	G	KOAc	CHCl ₃	75 96:4

[a] General conditions: 7a (0.12 mmol), 2a or 8a (0.10 mmol), NHC (0.02 mmol), base (0.14 mmol), additive (0.02 mmol), DQ (0.12 mmol), solvent (1.0 mL), rt, 24 h. [b] Isolated yield of 7 after purification by column chromatography. [c] The *er* was determined via HPLC on a chiral stationary phase. [d] 7a (0.12 mmol), 8a (0.10 mmol), C (0.01 mmol), KOAc (0.13 mmol), G (0.01 mmol), DQ (0.12 mmol), CHCl₃ (1.0 mL), 0 °C, 48 h.

Figure 3. Scope of pyrrole aldehydes 7 and isatins 8. General conditions: 7 (0.12 mmol), 8 (0.10 mmol), C (0.01 mmol), KOAc (0.13 mmol), G (0.01 mmol), DQ (0.12 mmol), CHCl₃ (1.0 mL), 0°C, 48 h. [a] The reaction was carried out at a 1.0 mmol scale based on 8a. [b] Toluene (1.0 mL) was used as the reaction solvent and the reaction was stirred at 40°C for 48 h.

After suitable conditions were found, the scope was extended to pyrrole aldehydes (7) and isatins (8) (Figure 3). Substituents on the 4-position of the pyrrole aldehyde were well tolerated (Figure 3, 9 b,c). Substitution on the 3-position of the pyrrole aldehyde resulted in drops on the product enantioselectivities, with reaction yields unaffected (9 d). Substitution on the 5-position of the pyrrole aldehyde could deactivate the nucleophilicity of its N-heteroaromatic ring, with the product afforded in only moderate yields (9 e). Trt-protected isatin substrates bearing different substituents or substitution patterns on the benzene rings all worked well (9f to 9 u).

The indole protecting groups on the chiral molecules 3a and 9a could be effectively removed to give the free oxindole products 10 and 11 in good yields, although the optical purities decreased slightly (Table 3). We also examined the anti-bacterial activities of the afforded chiral *N,O*-acetal products using *Ralstonia solanacearum* (abbreviated as *Rs*) as the target bacterium. *Rs* can cause blight on plant leaves and results in the death of a variety of crops.^[54,55] Thiodiazole- copper and bismertiazol are two of the most frequently used commercial agrichemicals to control these diseases. Several of

the afforded chiral *N,O*-acetal products from our approach exhibit superior antibacterial activities against *Rs* over the commercially available agrichemicals. These results encourage us to further investigate the bioactivities of our chiral *N,O*-acetal products in order to obtain novel agrichemicals with better efficiencies and less pollution for effective plant protection.

Conclusion

In summary, we have developed a new approach for the activation of nitrogen atoms in heteroarenes for enantioselective reactions. Through the addition of a carbene catalyst to the aldehyde moiety of indole and pyrrole aldehydes under oxidative conditions, the nitrogen atom in the aromatic p-system is activated. This carbene-catalyzed activation generates unprecedented aza-fulvene-type acylazolium intermediates that enantioselectively react with ketones to form *N,O*-acetals in excellent yields and *er* values. The reactions are found to be general and a broad range of N-heteroaromatic aldehydes and electron-deficient ketones reacted effectively. The chiral *N,O*-acetal products obtained by our strategy exhibit encouraging antibacterial activities against *Rs* and are valuable in the development of novel chiral agri-

chemicals for plant protection. Our study constitutes the first NHC-catalyzed activation of nitrogen atoms that are part of aromatic p-rings. It expands the power of carbene catalysis in achieving asymmetric reactions involving aromatic skeletons.

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Table 3: Synthetic transformations and antibacterial activities of the *N,O*-acetal products.

Removal of the N-Bn group:
$\xrightarrow[\text{PhCl, 130 } ^\circ\text{C, 15 h}]{\text{NBS, AIBN}}$
3a, 99:1 er		10, 70%, 98:2 er	
Removal of the N-Trt group:
$\xrightarrow[\text{PhOCH}_3, 120 } ^\circ\text{C, 24 h}]{\text{AcOH}}$
9a, 96:4 er		11, 84%, 92:8 er	
compound	<i>Ralstonia solanacearum</i> (Rs) inhibition rate (%)		
	100 mgmL ⁻¹	50 mgmL ⁻¹	
3a	86.67 ± 1.76	81.88 ± 0.55	
3c	83.91 ± 5.05	80.74 ± 4.22	
3h	71.55 ± 9.02	59.53 ± 5.24	
3i	89.49 ± 8.26	85.88 ± 3.70	
3j	89.08 ± 5.15	88.17 ± 1.01	
4a	76.61 ± 6.38	68.72 ± 0.68	
4b	88.22 ± 0.98	83.01 ± 8.89	
9a	82.03 ± 9.22	77.04 ± 8.64	
9e	64.06 ± 4.71	55.74 ± 4.78	
9g	63.00 ± 8.85	55.82 ± 2.99	
thiodiazole-copper	46.82 ± 3.46	28.58 ± 4.42	
bismertiazol	62.42 ± 1.63	53.25 ± 3.10	

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Conflict of interest

The authors declare no conflict of interest.

Keywords: activation of aromatic nitrogen · acylazolium · aza-fulvenes · *N,O*-acetals · N-heterocyclic carbenes

- [1] H.-G. Cheng, L.-Q. Lu, T. Wang, Q.-Q. Yang, X.-P. Liu, Y. Li, Q.-H. Deng, J.-R. Chen, W.-J. Xiao, *Angew. Chem. Int. Ed.* 2013, **52**, 3250–3254; *Angew. Chem.* 2013, **125**, 3332–3336.
- [2] L. Wang, J. Zhou, T.-M. Ding, Z.-Q. Yan, S.-H. Hou, G.-D. Zhu, S.-Y. Zhang, *Org. Lett.* 2019, **21**, 2795–2799.
- [3] J. March, *Advanced Organic Chemistry Reactions, Mechanisms and Structure*, 3rd ed., Wiley, Hoboken, 1985.
- [4] Y.-Y. Huang, C. Cai, X. Yang, Z.-C. Lv, U. Schneider, *ACSCatal.* 2016, **6**, 5747–5763.
- [5] S. Warriner in *Science of Synthesis*, Vol. 30 (Ed.: D. Bellus), Thieme, Stuttgart, 2007, p. 7.
- [6] L. Zhang, J.-H. Dong, X.-X. Xu, Q. Liu, *Chem. Rev.* 2016, **116**, 287–322.

- [7] J. T. Link, S. Raghavan, S. J. Danishefsky, *J. Am. Chem. Soc.* 1995, **117**, 552–553.
- [8] J. T. Link, S. Raghavan, M. Gallant, T. C. Chou, L. M. Ballas, *J. Am. Chem. Soc.* 1996, **118**, 2825–2842.
- [9] H. Chen, J. Bai, Z. F. Fang, S. S. Yu, S. G. Ma, S. Xu, Y. Li, J. Qu, J. H. Ren, L. Li, Y. K. Si, X. G. Chen, *J. Nat. Prod.* 2011, **74**, 2438–2445.
- [10] G. Li, F. R. Fronczek, J. C. Antilla, *J. Am. Chem. Soc.* 2008, **130**, 12216–12217.
- [11] S. Vellalath, I. Čorić, B. List, *Angew. Chem. Int. Ed.* 2010, **49**, 9749–9752; *Angew. Chem.* 2010, **122**, 9943–9946.
- [12] T. Arai, K. Tsuchiya, E. Matsumura, *Org. Lett.* 2015, **17**, 2416–2419.
- [13] F. Jiang, D. Zhao, X. Yang, F.-R. Yuan, G. J. Mei, F. Shi, *ACS Catal.* 2017, **7**, 6984–6989.
- [14] D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* 2007, **107**, 5606–5655.
- [15] N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem. Int. Ed.* 2007, **46**, 2988–3000; *Angew. Chem.* 2007, **119**, 3046–3058.
- [16] V. Nair, S. Vellalath, B. P. Babu, *Chem. Soc. Rev.* 2008, **37**, 2691–2698.
- [17] A. T. Biju, N. Kuhl, F. Glorius, *Acc. Chem. Res.* 2011, **44**, 1182–1195.
- [18] J. Izquierdo, G. E. Hutson, D. T. Cohen, K. A. Scheidt, *Angew. Chem. Int. Ed.* 2012, **51**, 11686–11698; *Angew. Chem.* 2012, **124**, 11854–11866.
- [19] S. J. Ryan, L. Candish, D. W. Lupton, *Chem. Soc. Rev.* 2013, **42**, 4906–4917.
- [20] S. De Sarkar, A. Biswas, R. C. Samanta, A. Studer, *Chem. Eur. J.* 2013, **19**, 4664–4678.
- [21] M. N. Hopkinson, C. Richter, M. Schedler, F. Glorius, *Nature* 2014, **510**, 485–496.
- [22] J. Mahatthananchai, J. W. Bode, *Acc. Chem. Res.* 2014, **47**, 696–707.
- [23] D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* 2015, **115**, 9307–9387.
- [24] M. H. Wang, K. A. Scheidt, *Angew. Chem. Int. Ed.* 2016, **55**, 14912–14922; *Angew. Chem.* 2016, **128**, 15134–15145.
- [25] X. Chen, Q. Liu, P. Chauhan, D. Enders, *Angew. Chem. Int. Ed.* 2018, **57**, 3862–3873; *Angew. Chem.* 2018, **130**, 3924–3935.
- [26] Z. Wang, D. Pan, T. Li, Z. Jin, *Asian J. Chem.* 2018, **13**, 2149–2163.
- [27] X. Chen, H. Wang, K. Doitomi, C. Y. Ooi, P. Zheng, W. Liu, H. Guo, S. Yang, B.-A. Song, H. Hirao, Y. R. Chi, *Nat. Commun.* 2016, **8**, 15598.
- [28] A. Lee, J. L. Zhu, T. Feoktistova, A. C. Brueckner, P. Cheong, K. A. Scheidt, *Angew. Chem. Int. Ed.* 2019, **58**, 5941–5945; *Angew. Chem.* 2019, **131**, 6002–6006.
- [29] X. Chen, S. Yang, B.-A. Song, Y. R. Chi, *Angew. Chem. Int. Ed.* 2013, **52**, 11134–11137; *Angew. Chem.* 2013, **125**, 11340–11343.
- [30] D. Janssen-Mgller, S. Singha, T. Olyschl-ger, C. G. Daniliuc, F. Glorius, *Org. Lett.* 2016, **18**, 4444–4447.
- [31] D.-F. Chen, T. Rovis, *Synthesis* 2017, **49**, 293–298.
- [32] J. Cheng, J. Sun, J. Yan, S. Yang, P. Zheng, Z. Jin, Y. R. Chi, *J. Org. Chem.* 2017, **82**, 13342–13347.
- [33] H. Wang, X. Chen, Y. Li, J. Wang, S. Wu, W. Xue, S. Yang, Y. R. Chi, *Org. Lett.* 2018, **20**, 333–336.
- [34] M. Bandini, A. Eichholzer, *Angew. Chem. Int. Ed.* 2009, **48**, 9608–9644; *Angew. Chem.* 2009, **121**, 9786–9824.
- [35] S. Lancianesi, A. Palmieri, M. Petrini, *Chem. Rev.* 2014, **114**, 7108–7149.
- [36] R. Dalpozzo, *Chem. Soc. Rev.* 2015, **44**, 742–778.
- [37] S. Lakhdar, M. Westermaier, F. Terrier, R. Goumont, T. Boubaker, A. R. Ofial, H. Mayr, *J. Org. Chem.* 2006, **71**, 9088–9095.
- [38] N. Otero, M. Mandado, R. A. Mosquera, *J. Phys. Chem. A* 2007, **111**, 5557–5562.

- [39] A. Przydacz, A. Skrzyńska, Ł. Albrecht, *Angew. Chem. Int. Ed.* 2019, **58**, 63–73; *Angew. Chem.* 2019, **131**, 64–75.
- [40] B.-X. Xiao, X.-Y. Gao, W. Du, Y.-C. Chen, *Chem. Eur. J.* 2019, **25**, 1607–1613.
- [41] M. Watanabe, T. Kobayashi, S. Kajigaeshi, S. Kanemasa, *Chem. Lett.* 1975, **4**, 607–610.
- [42] E. Galeazzi, A. Guzman, G. Rodriguez, J. M. Muchowski, *J. Org. Chem.* 1993, **58**, 974–976.
- [43] J. Barluenga, J. García-Rodríguez, S. Martínez, A. L. Suárez-Sobrinho, M. Tomàs, *Chem. Eur. J.* 2006, **12**, 3201–3210.
- [44] A. R. Katritzky, S. K. Singh, S. Bobrov, *J. Org. Chem.* 2004, **69**, 9313–9315.
- [45] G. Bertuzzi, M. K. Thørgersen, M. Giardinetti, A. Vidal-Albalat, A. Simon, K. N. Houk, K. A. Jørgensen, *J. Am. Chem. Soc.* 2019, **141**, 3288–3297.
- [46] S. De Sarkar, S. Grimme, A. Studer, *J. Am. Chem. Soc.* 2010, **132**, 1190–1191.
- [47] M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* 2006, **128**, 8418–8420.
- [48] S. Kobayashi, T. Kinoshita, H. Uehara, T. Sudo, I. Ryu, *Org. Lett.* 2009, **11**, 3934–3937.
- [49] M. S. Kerr, J. Read de Alaniz, T. Rovis, *J. Org. Chem.* 2005, **70**, 5725–5728.
- [50] C. Zhao, F. Li, J. Wang, *Angew. Chem. Int. Ed.* 2016, **55**, 1820–1824; *Angew. Chem.* 2016, **128**, 1852–1856.
- [51] L. Pitzer, F. Schafers, F. Glorius, *Angew. Chem. Int. Ed.* 2019, **58**, 8572–8576; *Angew. Chem.* 2019, **131**, 8660–8664.
- [52] For detailed studies on the product stabilities and the reaction sensitivities, see the Supporting Information.
- [53] For pioneering studies, see: D. E. A. Raup, C. B. David, D. Holte, K. A. Scheidt, *Nat. Chem.* 2010, **2**, 766–771.
- [54] M. Nakano, T. Mukaihara, *Plant Cell Physiol.* 2018, **59**, 2576–2589.
- [55] Y. Ishikawa, Y. Murai, M. Sakata, S. Mori, S. Matsuo, W. Senuma, K. Ohnishi, Y. Hikichi, K. Kai, *ACS Chem. Biol.* 2019, **14**, 1546–1555.
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