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Organocatalytic enantioselective allylic alkylation of MBH carbonates with β-keto esters†

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The highly stereoselective allylic alkylation of Morita–Baylis–Hillman carbonates with β-ketoesters catalysed by β-ICD is described. The corresponding products containing two adjacent quaternary and tertiary carbon centers were obtained in good yields with high diastereoselectivity (up to 10 : 1 dr) and enantioselectivity (up to 95% ee).

The formation of all-carbon quaternary stereocenters represents one of the most difficult contemporary challenges in synthetic organic chemistry. This is particularly difficult due to synthetic impediment arising from the steric congestion imposed by the four attached carbons and the limited number of carbon–carbon bond-forming reactions.[1,2] However, the presence of these motifs is common in natural products and pharmacologically active substances.[3] Several approaches can be used to form all-carbon quaternary stereocenters including Diels–Alder reactions and other cycloadditions, carbon-acylation reactions, Mannich reactions, aldol reactions, conjugate additions, Robinson annulations, Heck reactions, metal-catalyzed diene, enyne cyclizations, *etc.*[4] Other important modern strategies suitable for accessing all-carbon quaternary stereocenters rely on Pd-catalyzed asymmetric alkylations[5] and decarboxylative allylic alkylations,[6] Cu-catalyzed methods,[7] and Mo-[8] and Ir-[9,1a,b] catalyzed allylic alkylations.

Also, the asymmetric conjugate addition reaction is of special importance among various synthetic strategies used for the construction of congested centers. In this area, not only methods *via* transition metal catalysis have been developed,[10,2c] but also alternative organocatalytic methods utilizing Morita–Baylis–Hillman (MBH) adducts in asymmetric allylic alkylation (AAA) reactions have become popular.[11] While the vast majority of literature from the area of Lewis base-catalyzed AAA methods deals with the preparation of various chiral compounds containing nitrogen,[12] oxygen,[13] other heteroatoms[14] or tertiary carbon,[15] methods for the preparation of compounds with all-carbon quaternary stereocenters are scarce.[16]

Readily available β-ketoesters represent a suitable structural motif, which has been already applied for the construction of quaternary carbon centers.[1a,b,7a,17] With respect to the above mentioned and our interest in the development of enantioselective organocatalytic methods,[18] we set out to explore the application of the MBH adducts as an electrophilic alkylation partner with β-ketoesters in the AAA reaction. Herein, we wish to report an enantioselective and regiodivergent allylic alkylation of α-substituted β-ketoesters with the MBH carbonates *via* SN2′–SN2′ pathway using a simple and commercially available Hatakeyama's catalyst, β-ICD.[19]

At the outset of our studies of allylic reactions of MBH adducts, we consider the use of ethyl 2-oxocyclopentane-1-carboxylate (**3a**) as a prenucleophile together with 2-(methoxycarbonyl)-1-phenylallyl *tert*-butyl carbonate (**2a**) initiated by 10 mol% of β-ICD as a nucleophilic tertiary amine catalyst. The reaction performed either in MTBE or in toluene went to completion in less than 16 h with low regioselectivity (ratio of γ-/β-adduct 3 : 1) and moderate enantioselectivity (entries 1 and 2, Table 1).

Substitution of the ester moiety at the β-oxoester with the sterically-demanding *tert*-butyl group (entry 3, Table 1) gave the desired product with a similar regioselectivity, but higher enantioselectivity (82% ee). A further change at the β-oxoester moiety, specifically the substitution of the cyclopentanone ring with the more rigid 2,3-dihydro-1-oxo-1*H*-indene, showed significant effect on the regioselectivity and diastereoselectivity of the allylation reaction (entries 5 and 6). On the other hand, no reaction was observed when the carbonate moiety (OBoc) was replaced with OAc (entry 7).

In order to verify the appropriateness of the reaction conditions, we subsequently performed screening of other com-

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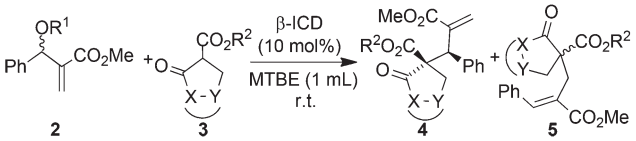
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of **4aa–aj**, **5aa–5ad**, **6a–c**, **7a**, chiral HPLC chromatograms of **4aa–aj**, **5aa–5ad**, **6a–c**, **7a**, X-ray crystallographic data for **4cd**, **6b** (CIF) and a spectroscopic study of absolute configuration **4cd**, **5aa**. CCDC 953269 and 953270. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob00682h

Table 1 Initial AAA of Morita–Baylis–Hillman esters **2** and β-oxoesters **3**[a]



Entry	X–Y	R^1	R^2	Solvent	Time (h)	dr[b]	Yield of **4**/**5** (%)	ee[c] (%)
1	C_2H_4	Boc	Et	Toluene	16	2 : 1	42/15	66
2	C_2H_4	Boc	Et	MTBE	16	2 : 1	43/13	58
3	C_2H_4	Boc	*t*-Bu	MTBE	20	5 : 2	47/11	82
4	C_6H_4	Boc	Me	MTBE	16	1 : 1	81[d]	56/64
5	C_6H_4	Boc	*t*-Bu	Toluene	22	3 : 1	60/10	89
6	C_6H_4	Boc	*t*-Bu	MTBE	20	5 : 1	70	90
7	C_6H_4	Ac	*t*-Bu	MTBE	120	—	n.d.	—

[a] In a vial **2** (1.1 equiv.), catalyst (0.1 equiv.) and **3** were added in MTBE (1 mL). [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Determined by chiral HPLC. [d] Yield of the mixture of diastereomers (3 : 2 ratio).

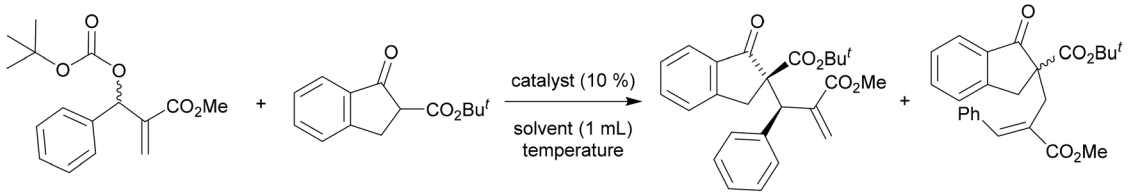
mercially available tertiary amine catalysts, used in AAA reactions in the prior study[16] (Table 2). None of the cinchona alkaloids and C_2-symmetric (bis)cinchona alkaloid derivatives tested showed significant effectiveness in the reported allylation reaction. For example, the cinchonidine-catalyzed model reaction afforded the desired product in 20% yield (45% conversion in 5 days was observed) with moderate diastereoselectivity (dr 3 : 1) and acceptable enantioselectivity (84% ee, entry 3, Table 2). In connection with the previous study, we focused on the dependence of reaction efficiency on catalyst loading. Interestingly, only slight drops in diastereoselectivity and enantioselectivity were observed when 5 mol% of β-ICD (**IV**) was used (entry 16). On the other hand, using 2 mol% of the catalyst led to significantly lower conversion of starting materials into the corresponding allylic product (entry 17). Next, we screened different solvents and temperature-dependence in order to achieve the corresponding allylic product (**4ad**) in good yields with high diastereo- and enantioselectivity. Screening of reaction solvents revealed that the model AAA reaction between **2a** and **3d** catalyzed by β-ICD performed well in ether solvents (THF and MTBE), where a significant drop in formation of β-adduct (Michael adduct) compared to toluene commonly used in AAA reactions was observed. The best results with respect to efficiency and stereoselectivity of the reaction were obtained in MTBE (entry 6, Table 2). The use of chlorinated solvents, such as DCM, led to a drop in yield and stereoselectivity of the corresponding product **4ad** (entry 7, Table 2).

On the other hand, no reaction was observed when polar and protic solvents were used (MeCN, MeOH, entries 10 and 11). It should also be noted that the stereocontrol of the reaction compared to the efficiency is only slightly temperature dependent (entries 13 and 14). Moreover, a significant rise of β-selectivity in non-polar solvents at higher reaction temperature was observed (entry 15 *vs.* 4).

After obtaining the optimized conditions, we turned our attention to the scope of the reaction using differently substituted MBH carbonates (**2a–l**, Table 3) and oxoesters (**3a–j**, Table 4). In order to study the scope of the AAA reaction, various MBH carbonates **5** including changes on the aromatic ring in the γ-position and the electrodeficient moiety at C-1 were introduced. In almost all cases of substitution of the aromatic moiety (R^1) with either electron-withdrawing or -donating groups as well as the change into heteroaryl group, the efficiency and stereocontrol of the AAA reaction were not significantly changed and the corresponding products **4ae–ee** were isolated as single diastereomers in good yields with high enantioselectivity (entries 1–5, Table 3). For example, β-ICD in MTBE catalyzed the AAA reaction between methyl 2-{[(*tert*-butoxycarbonyl)oxy](4-methoxyphenyl)methyl}acrylate (**2e**) and *tert*-butyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (**3e**) with good diastereoselectivity (dr 5 : 1) and the α-allylated product (**4ee**) was isolated in 85% yield as a single diastereomer with 91% ee (entry 5). An important drop in stereoselectivity, especially in enantiocontrol of the reaction, was observed in the presence of strongly electron-withdrawing groups, such as the nitro group (dr 3 : 1, 71% ee, entry 8). Taking into account the high reactivity of compound **2h** towards conjugate addition and already reported results of AAA reactions using **2a** and α,α-cyanophenylacetate at lowered temperature (16% ee),[16a] our observation with **4he** could be satisfying. A significant effect on the efficiency, diastereo- and enantioselectivity of the reaction was also observed when sterically demanding MBH carbonate **2i** was subjected to the reaction (entry 9). Moreover, the replacement of the aryl moiety with an olefin substituent at γ-position of MBH carbonate led to a complex mixture, where the desired product was not isolated from (entry 11).

Next we further examined β-ketoester derivatives (**3**) under the optimized conditions (Table 4). The alkyl group of the ester moiety significantly influenced the reaction efficiency and stereoselectivity of the AAA reaction. In general, sterically demanding ester moieties, such as *tert*-butyl and adamant-1-yl, afforded the corresponding allylated products (**4ad–ae**) in acceptable yields with good diastereoselectivity (dr 4 : 1–5 : 1) and high enantioselectivity (85–90% ee, entries 4 and 5). On the other hand, when primary and secondary alkyl esters

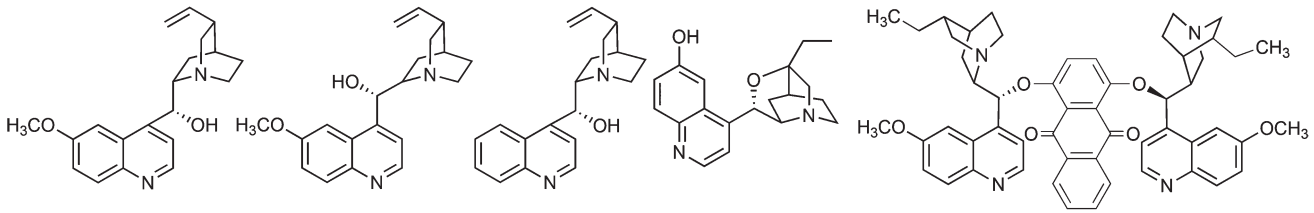
Table 2 Optimization studies focused on solvent, catalyst and temperature influences on AAA of MBH carbonate **2a** and β-ketoester **3e**[a]



2a **3d** **4ad** **5ad**

Entry	Solvent	Catalyst	Temperature (°C)	Time (h)	Conversion (%)	dr[b]	Yield of **4e**/**5e** (%)	ee[c] (%)
1	Toluene	I	25	120	45	3 : 1	20/—	7
2	Toluene	II	25	120	50	2 : 1	25/—	59
3	Toluene	III	25	120	45	3 : 1	20/—	84
4	Toluene	IV	25	22	100	3 : 1	60/10	89
5	Toluene	V	25	120	0	—	n.d.	—
6	MTBE	IV	25	20	100	5 : 1	70/—	90
7	DCM	IV	25	20	100	2 : 1	52/13	73
8	$CHCl_3$	IV	25	20	100	2 : 1	25/18	65
9	*p*-Xylene	IV	25	20	100	2 : 1	20/17	87
10	MeCN	IV	25	20	100	—	n.d.	—
11	MeOH	IV	25	120	0	—	n.d.	—
12	THF	IV	25	7	100	3 : 1	56/—	87
13	THF	IV	0	20	100	5 : 1	63/—	90
14	THF	IV	−20	60	100	5 : 1	64/—	86
15	Toluene	IV	50	8	100	3 : 1	50/19	88
16	MTBE	IV	25	30	100	4 : 1	52/—	90[d]
17	MTBE	IV	25	70	100	4 : 1	32/—	85[e]

[a] In a vial **2** (1.1 equiv.), catalyst (0.1 equiv.) and **3** were added in solvent (1 mL). [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Determined by chiral HPLC. [d] 5% mol catalyst loading. [e] 2% mol catalyst loading.



I **II** **III** **IV** **V**

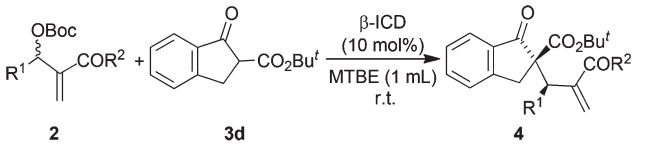
(**3f–h**) were employed, diastereo- and enantiocontrol of the reaction dropped down (entries 6–8). Moreover, the isolated products **4ag–ah** were obtained as a mixture of diastereoisomers after column purification. It is noteworthy that a significant influence of ring-expansion in cyclic β-ketoesters (**3i,j**) to diastereoselectivity of the reported AAA reaction was observed (entries 9 and 10). For example, AAA reaction between ethyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (**3i**) and methyl 2-{[(*tert*-butoxycarbonyl)oxy](4-methoxyphenyl)methyl}acrylate (**2a**) under the optimized conditions afforded the corresponding allylated α-ketoester (**4aj**) as a single diastereomer in 64% yield with high diastereoselectivity (dr 5 : 1) and good enantioselectivity (79% ee, entry 10).

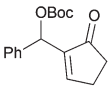
Unfortunately the AAA reaction performed with less sterically demanding oxoesters containing a cyclopentanone moiety (**3a–c**) afforded a significant amount of β-adduct (11–40% yield, entries 1–3). For example, treatment of **2a** with **3a** furnished, in addition to **4aa** (45% yield, 58% ee), by-product **5aa** in 13% yield as a racemic mixture. *E*-Configuration of **5aa** at the alkene moiety was determined based on 1D NOE NMR experiments (for more details see ESI†).

In order to ascertain the absolute configuration of the allylated β-ketoesters (**4**), we performed a single X-ray diffraction analysis of compound **4cd**,[20] obtained from the reaction of **2c** and **3e**. As shown in Fig. 1, both stereogenic centers (C2 and C11) have (*R*)-absolute configuration. This configuration corresponds also to the data obtained from 1D gNOESY NMR experiments (for more information see ESI†).

Next, we performed experiments to examine the dependence of enantiocontrol during AAA reaction in connection with enantiomeric purity of starting material **2**. In the model reaction of **2a** with **3d**, we measured the enantiomeric purity of the allylated product (**4ad**) and the MBH carbonate (**2a**) at different conversions (Fig. 1, ESI†). Moreover, we accomplished an AAA reaction of enantiomerically enriched **2a** (77% ee) with **4ad** (for more details see ESI†). All the collected data clearly indicate very slight changes (1–2%) in enantioselectivity (90% ee) of the final product **4ad** and significant kinetic resolution

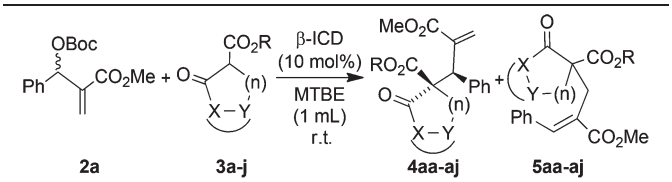
Table 3 Substrate scope of AAA screened on the reaction of β-oxoester **3e** with various MBH carbonates **2**[a]



Entry	R^1	R^2	Time (h)	dr[b]	Yield (%)	ee[c] (%)
1	Ph	OMe	20	5 : 1	70	90
2	*p*-ClPh	OMe	19	4 : 1	60	88
3	*p*-BrPh	OMe	20	4 : 1	60	93
4	*o*-BrPh	OMe	14	3 : 1	21	78
5	*p*-MeOPh	OMe	18	4 : 1	82	91
6	*p*-MePh	OMe	16	4 : 1	50	88
7	1-Thienyl	OMe	19	5 : 1	70	83
8	*p*-NO_2Ph	OMe	17	3 : 1	70	71
9	1-Naphthyl	OMe	20	10 : 1	42	95
10	Ph	Me	10	2 : 1	26 (46)[d]	91 (95)[e]
11	*E*-Styryl	OMe	16	—	n.d.[f]	—
12			120	—	n.d.	—

[a] In a vial **2** (1.1 equiv.), β-ICD (0.1 equiv.) and **3** were added in MTBE (1 mL). [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Determined by chiral HPLC. [d] Yield of the mixture of diastereomers (3 : 2 ratio). [e] ee of the minor diastereomer from the isolated mixture of diastereomers (ratio 3 : 2). [f] Unidentified mixture of products.

Table 4 Substrate screening of AAA using differently substituted oxo-esters **3**[a]



Entry	R	X–Y	*n*	Time (h)	dr[b]	Yield of **4**/**5** (%)	ee (%)[c]
1	Et	C_2H_4	CH_2	16	2 : 1	45/13	58
2	i-Pr	C_2H_4	CH_2	13	3 : 1	36/40	77
3	*t*-Bu	C_2H_4	CH_2	20	5 : 2	47/11	82
4	*t*-Bu	C_6H_4	CH_2	20	5 : 1	70	90
5	1-Adamantyl	C_6H_4	CH_2	13	4 : 1	50	85
6	i-Pr	C_6H_4	CH_2	15	2 : 1	40	69
7	Et	C_6H_4	CH_2	12	1 : 1	61[d]	65/71
8	Me	C_6H_4	CH_2	16	1 : 1	81[e]	56/64
9	*t*-Bu	C_6H_4	C_2H_4	50	10 : 1	40	84
10	Et	C_6H_4	C_2H_4	14	5 : 1	64	79

[a] In a vial **2** (1.1 equiv.), β-ICD (0.1 equiv.) and **3** were added in MTBE (1 mL). [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Determined by chiral HPLC. [d] Yield of the mixture of diastereomers (ratio 3 : 1). [e] Yield of the mixture of diastereomers (3 : 2 ratio).

of the MBH carbonate **2a**. Our observations are in full agreement with already reported data[15i] and the generally accepted mechanism pathway as well.

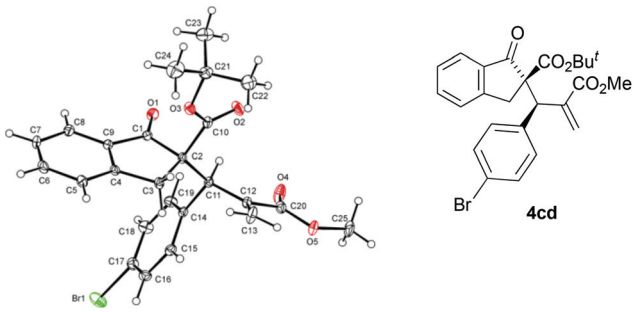
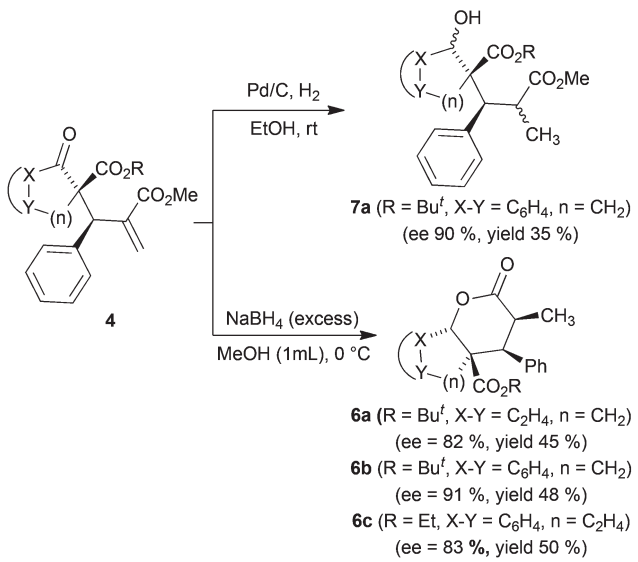


Fig. 1 View on one of the two symmetrically independent molecules of **4cd** with the atom numbering scheme. The displacement ellipsoids are drawn at the 50% probability level.



Scheme 1 Reduction of compound **4** to alcohol **7a** and lactones **6a–c**.

The versatility of the reaction has been demonstrated by the conversion of **4ac**, **4ad** and **4aj** into appropriate lactones **6** and conversion of **4ad** into alcohol **7a** (Scheme 1). A simple reduction of **4** by $NaBH_4$ in MeOH was accompanied by self-lactonization affording the corresponding lactones **6a–c** as single diastereomers. The absolute configuration (*S*-C2, *S*-C3, *R*-C4, *S*-C5) of lactone **6b** was determined using X-ray diffraction analysis (Fig. 2).[21]

Conclusions

To summarize, we have developed a regioselective organocatalytic allylic alkylation of β-ketoesters using MBH carbonates. The reaction catalyzed byβ-ICD affords the corresponding products containing vicinal tertiary and quaternary carbon centers in good yield with high diastereo- and enantioselectivity. Next, the allylated products can be further converted into valuable pyranose derivatives *via* reduction/

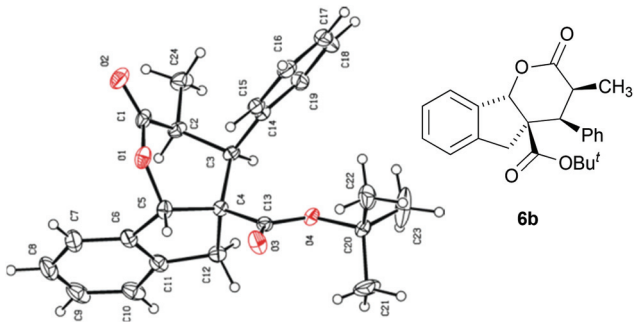


Fig. 2 View on one of the two symmetrically independent molecules of **6b** with the atom numbering scheme. The displacement ellipsoids are drawn at the 50% probability level.

lactonization tandem reaction with retained enantioselectivity. Mechanistic studies and synthetic applications of this methodology are currently ongoing in our laboratory.

Acknowledgements

We are grateful for the financial support from the Charles University Grant Agency (grant no. 427011).

Notes and references

1 For selected examples of recent articles focused on the formation of quaternary stereocenters, see: (*a*) W.-B. Liu, C. M. Reeves and B. M. Stoltz, *J. Am. Chem. Soc.*, 2013, **135**, 17298–17301; (*b*) W.-B. Liu, C. M. Reeves, S. C. Virgil and B. M. Stoltz, *J. Am. Chem. Soc.*, 2013, **135**, 10626–10629; (*c*) S. Hanessian, S. Dorich, A. K. Chattopadhyay and M. Büschleb, *J. Org. Chem.*, 2013, **78**, 8915–8921; (*d*) Y. Minko, M. Pasco, L. Lercher, M. Botoshansky and I. Marek, *Nature*, 2012, **490**, 522–526; (*e*) P. Jakubec, A. Hawkins, A. Felzmann and D. J. Dixon, *J. Am. Chem. Soc.*, 2012, **134**, 17482–17485; (*f*) R. R. Knowles, J. Carpenter, S. B. Blakey, A. Kayano, I. K. Mangion, C. J. Sinz and D. W. C. MacMillan, *Chem. Sci.*, 2011, **2**, 308–311.

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21 Crystallographic data (excluding structure factors) for the structure **6b** have been deposited with the Cambridge Crystallographic Data Centre with CCDC number 953270.

