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Room-Temperature Enantioselective C–H Iodination via Kinetic Resolution

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Abstract

The development of asymmetric C–H activation reactions through metal insertions remains in its infancy. The commonly used approach is the desymmetrization of prochiral C–H bonds on the same or different carbons of one achiral molecule using a chiral catalyst. Herein, we report a Pd-catalyzed enantioselective C–H activation reaction via kinetic resolution in which one of the enantiomers of the racemic substrates undergoes faster C–H insertion with the chiral catalysts thereby producing enantioenriched C–H functionalization products that are not accessible via desymmtrization of prochiral C–H bonds. The exceedingly high relative rate (k_{fast}/k_{slow} up to 244) and the subsequent iodination of the remaining enantiomerically enriched starting material using a chiral ligand with the opposite configuration allows for the conversion of both enantiomers of amines into enantiomerically pure iodinated amines.

A wide range of C–H activation reactions have emerged as promising tools for organic synthesis over the past three decades. However, the development of enantioselective C–H activation reactions has met with limited success in terms of efficiency and scope (1). Enantioselective carbene insertions of prochiral methylene C–H bonds adjacent to heteroatoms have been achieved in synthetically useful enantioselectivity (2). Asymmetric nitrene insertion has also been demonstrated in both diastereoselective and enantioselective fashion (3–6). Development of asymmetric C–H activation reactions using organometallic approach has also witnessed limited but encouraging progress. Combining C–H activation with a subsequent asymmetric carbometalation onto double bonds elegantly connects C–H functionalization reactions to asymmetric catalysis (7, 8). An early example of atropselective alkylation in moderate enantioselectivity (49% ee) was reported (9). Recently, Pd-catalyzed desymmetrization of prochiral C–H bonds has been achieved with excellent levels of enantioselectivity (10–14). However, the requirement for the presence of two chemically identical groups necessarily limits the structural diversity of the chiral products, preventing the broad application of this method in asymmetric synthesis.

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Supplementary Materials:
Materials and Methods
NMR Spectra
HPLC Spectra
References (*31–35*)

Chiral amines are one of the most prevalent motifs in bioactive natural products, drug molecules, and chiral catalysts. Despite remarkable progress in development of catalytic enantioselective methods for synthesis of chiral amines (15, 16), the use of methods based on chiral auxiliaries (17), classic resolution, or enzymatic kinetic resolution (18) is often the method of choice in applications. Notably, the nonenzymatic kinetic resolution of amines via asymmetric acyl transfer catalysts remains a significant challenge when compared to the analogous kinetic resolution of alcohols (19–21). In our efforts to develop alternative methods for the asymmetric synthesis of chiral amines, we recently achieved the enantioselective C–H iodination of triflyl-protected benzylamines via desymmetrization (12). However, this approach can only access diarylmethylamines containing two identical aryl groups. We envisioned that a kinetic resolution process via an enantioselective C–H iodination of arylalkylamines could overcome this limitation, providing access to a wide range of chiral α-branched benzylamines. Practically, this type of process would not only lead to the resolution of racemic amines but also concomitantly introduces a new functional handle for the further elaboration of the product. Conceptually, the chiral recognition required in kinetic resolution is fundamentally different to that in the desymmetrization process. The catalyst needs to preferentially recognize one of the enantiomeric substrates in kinetic resolution instead of one of the prochiral groups within the same substrate as in desymmetrization. Despite the landmark success in kinetic resolution via the Jacobsen's epoxide opening process (22) and the pioneering work on Pd(II)-catalyzed asymmetric oxidation of racemic alcohols (23, 24), kinetic resolution via a Pd-catalyzed C–H activation reaction remains to be established.

Herein we report the discovery of a highly efficient kinetic resolution of chiral amines via Pd-catalyzed C–H iodination with selectivities reaching up to 244 (Fig. 1C). In addition to simple arylalkylamines, a wide range of β-amino acids and β-amino alcohols are compatible with this reaction. The use of ambient temperature provides a significant operational advantage over nonenzymatic acylative kinetic resolution reactions, which often require low temperature operations. We further demonstrate that the remaining starting material can subsequently be iodinated using a MPAA ligand with opposite configuration to give *ortho*-iodinated amines in high ees, thus rendering this technology a versatile and novel method for converting both enantiomers of the racemic amines into *ortho*-iodinated chiral benzylamines. The newly introduced *ortho*-iodides are a useful functional handle, allowing the products to be converted into a broad range of chiral amines. Notably, a *de novo* synthesis of these *ortho*-iodinated chiral benzylamines generally relies on the use of *ortho*-iodinated benzaldehyde derivatives, which require multiple step preparations (25).

Our experimental design was based on a previous finding that a *mono*-protected amino acid ligand (MPAA) can effectively control the stereochemistry in Pd-catalyzed asymmetric insertion into prochiral C–H bonds on different carbon centers, leading to desymmetrization (11). This led us to hypothesize that the chiral catalyst assembled from a MPAA and Pd(II) species could preferentially recognize one enantiomer of a racemic substrate during the C–H activation step. If successful, a wide range of C–H activation reactions could potentially be developed into practical tools for asymmetric catalysis via kinetic resolution. Due to its compatibility with low reaction temperatures, we selected our recently developed C–H

iodination as a model reaction to investigate the feasibility of achieving kinetic resolution of α-branched benzylamines at room temperature. Thus, 1-(*o*-tolyl)ethylamine, protected by a triflyl group (**1a**), was subjected to our iodination conditions in the presence of various *mono*-protected amino acid ligands (Table 1). We found the use of benzoyl-protected L-2-aminopentanoic acid (norvaline) as the chiral ligand, Pd(II)-catalyzed iodination of **1a** proceeds with promising selectivity (entry 1, *s* = 17.6). A minor increase in steric hindrance on the side chain when leucine is used improves the selectivity to 50 (entries 2–3). However, an even bulkier neopentyl side chain affects the selectivity adversely (entry 4). Interestingly, the introduction of a secondary *i*-propyl side chain gives good selectivity (entry 5, *s* = 30.8). Further increase in steric hindrance on the secondary side chain also reduces the selectivity (entry 6). Extensive efforts to improve the selectivity by using a substituted *N*-benzoyl protecting group were unsuccessful (entries 7–12). We also found that acetyl, trifluoroacetyl and Boc protecting groups are inferior to benzoyl-type protecting group (entries 13–15). We further found that an increase in the reaction concentration improves the selectivity to 62.0 (entry 16). Finally an optimum selectivity of 78.8 is obtained by running the reaction in a mixture of ^{t}amyl alcohol and DMSO with the ratio of 5 : 2.2 (entry 17). In this case, both the iodinated product and recovered starting material are obtained with high enantioselectivity (92% ee) at 50% conversion. The reaction also proceeds with 2 mol% Pd catalyst to reach a selectivity of 51.2, albeit at longer reaction times (entry 17).

To examine whether this method can be applied to prepare a broad range of chiral *ortho*-iodinated benzylamines, we subjected amines **1b-l** to the optimized conditions. Iodination of benzylamines **1a-c** gives good to excellent selectivity whereas the bulkier α-isobutyl and benzyl groups in **1d** and **1e** lead to a decrease in the selectivity factor to 25.0 and 13.8 respectively (entries 1–5). Iodination of benzylamine **1f** containing a cyclopropyl group proceeds with an excellent selectivity factor (entry 6, *s* 83.5). Arenes containing *ortho*-methoxy and fluoro groups are also iodinated with outstanding selectivity (entries 7–8, *s* 148 and 240 respectively). The presence of a *para*-chloro group on the aryl fragment in **1i** was well tolerated (entry 9, *s* 113). *Meta*- and *para*-methyl substituted arenes **1j** and **1k** are more suitable substrates than the *ortho*-methylarene **1a** affording excellent selectivity (entries 10–11, *s* 99.5 and 91.7 respectively). Iodination of **1l** containing 2-naphthyl group also proceeded with synthetically useful selectivity (entry 12, *s* 76). In general, the iodinated products were obtained with high levels of enantioselectivity (91–97% ee) with the exception of entries 3–5. To investigate whether the decrease of enantioselectivity with these substrates containing bulkier α-alkyls (entries 3–5) is a general phenomenon, we subjected **1m** containing α-butyl to the standard iodination conditions. The reaction proceeds with high enantioselectivity (entry 13, *s* 124), thus suggesting that the observed adverse effect of the bulky α-alkyl group is only associated with the *ortho*-methylbenzylamine substrates **1a-e**.

The significance of β-amino acids in pharmaceutical compounds prompted us to investigate whether our newly developed enantioselective iodination can be applied for the production of iodinated chiral β-amino acids. In spite of a number of highly creative asymmetric methods for making enantioenriched β-amino acids (26, 27), resolution is still frequently utilized due to the ease of preparing racemic β-amino acids by the Rodionov reaction. The

development of highly efficient catalysts to resolve racemic β-amino acids continues to attract significant attention (28–30). Using our methodology, β-phenyl-β-amino acid **4a** is iodinated under the standard conditions to give **6a** with excellent selectivity (*s*, 128). Substrates containing electron-donating groups at the *ortho*, *meta* and *para* positions of the β-phenyl groups are all iodinated with high selectivity factors ranging from 112 to 168 (entries 2–4). Electron-withdrawing groups on the β-phenyl rings are also compatible with this transformation affording selectivity factors as high as 244 (entries 5–7). In all cases, the iodinated amino acid derivatives are obtained with high levels of enantioselectivity (94–99% ee).

We were pleased to find that this enantioselective C–H activation method is also suitable for preparing *ortho*-iodinated chiral β-amino alcohols. 2-Phenyl amino alcohol **7a** is iodinated with a practically useful selectivity (*s*, 88). The *ortho*-methyl group in **7b** leads to a slight decrease the selectivity factor (*s*, 77.2) whereas 2-(*ortho*-fluoro)-phenyl and 2-naphthyl-amino alcohols were iodinated with excellent selectivity (*s*, 188 and 112 respectively).

To further demonstrate the versatility of this kinetic resolution process based on enantioselective C–H iodination, we developed a protocol to convert both enantiomers of the racemic amine substrates to the chiral iodinated amines in high enantiomeric purity. Thus, 1.0 gram of **1l** is subjected to the standard reaction conditions using the L-amino acid ligand to give 37% iodinated product **3l** (maximum 50% yield) with 95% ee (Fig. 2A). The recovered starting material **2l** with 69% ee is then iodinated using the D-amino acid ligand to give chiral amine **3l′** in 98% ee (Fig. 2A). The use of ligands possessing the opposite configuration to enantioselectively iodinate the enantiomerically enriched starting material could prove extremely useful when the selectivity factor is lower than 50 and the ee of the starting material is lower than 90% ee. To render this reaction synthetically useful, triflyl protected amine **2l** is readily deprotected and converted to benzoyl protected amine **10** under mild conditions without racemization (Fig. 2B). Finally, the chiral iodinated amine **3l** is converted to diverse range of amines, illustrating the broad utility of this method to access a diverse range of chiral amines (Fig. 2C).

In summary, we have developed a highly enantioselective C–H iodination reaction for kinetic resolution of arylalkylamines. A wide range of chiral *ortho*-iodinated α-branched benzylamines, β-amino acids, and amino alcohols can be prepared via this enantioselective C–H iodination reaction using an L-amino acid ligand. The enantiomerically enriched remaining starting material can also be enantioselectively iodinated using a D-amino acid ligand to give the opposite enantiomer of the iodinated amines in excellent enantioselectivity. Conceptually, development of enantioselective C–H activation reactions via kinetic resolution overcomes the limitation imposed by the desymmetrization approach which requires the presence of two chemically identical groups in the substrates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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One Sentence Summary

Enantioselective C–H iodination via kinetic resolution establishes a new avenue for developing asymmetric C–H activation reactions.

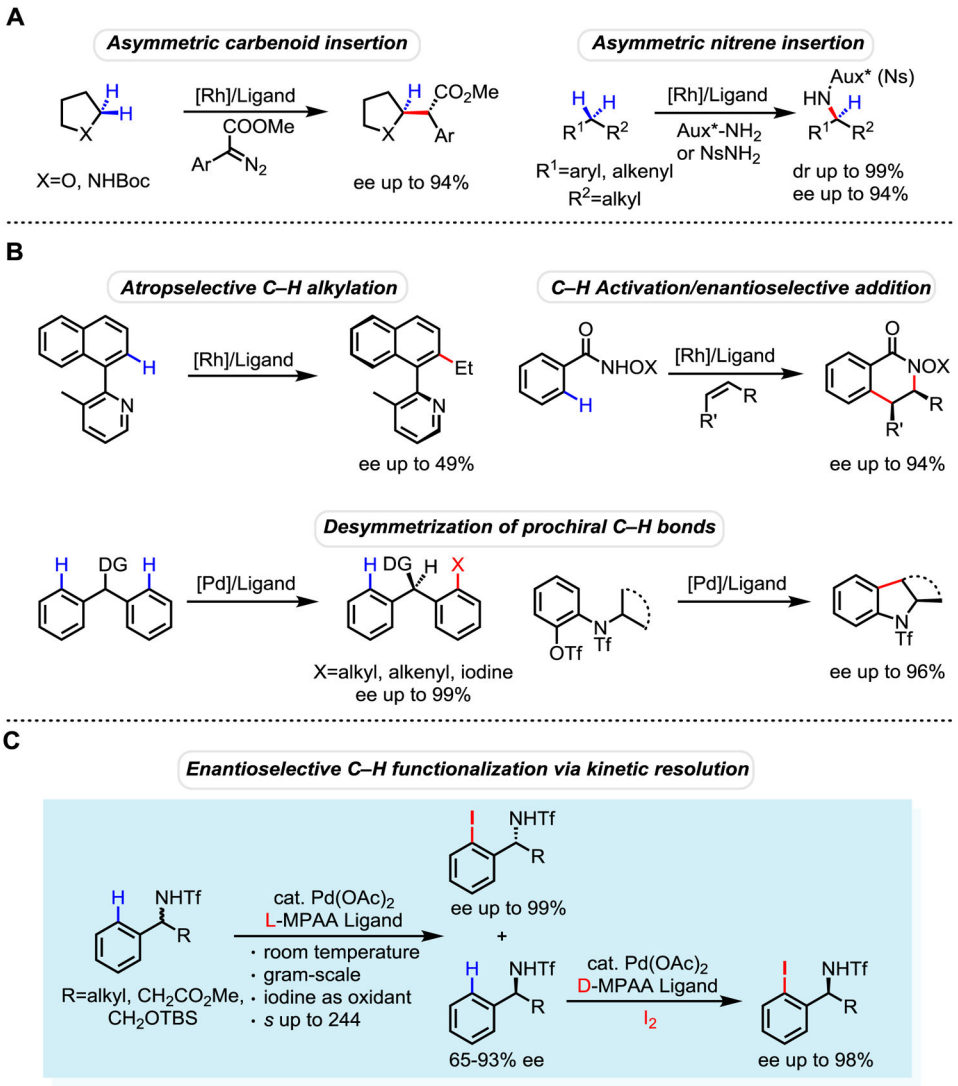

Fig. 1.

(**A**) Carbene and nitrene C–H insertions. (**B**) Three different organometallic approaches towards asymmetric C–H activation. (**C**) Enantioselective C–H activation via kinetic resolution.

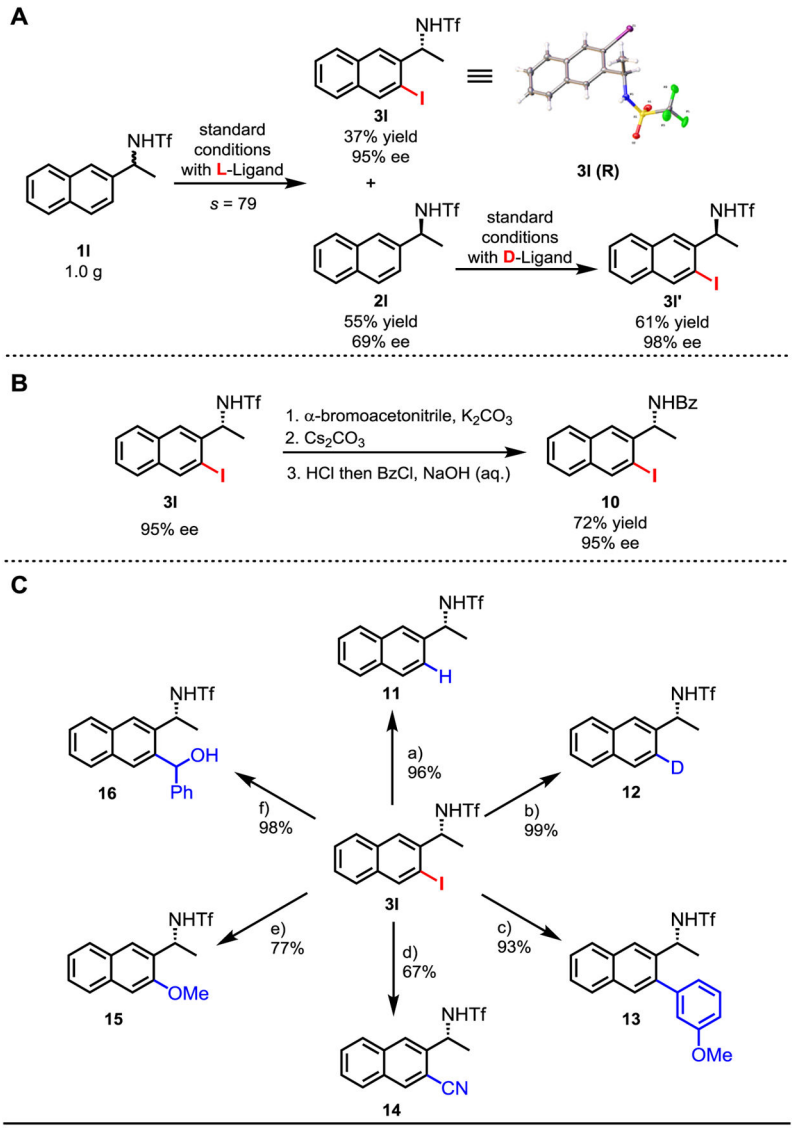

Fig. 2.

(**A**) Gram-scale synthesis and reaction with D-amino acid ligand. (**B**) Deprotection of the triflyl protecting group. (**C**) Functionalization of iodinated chiral amine **3l**.

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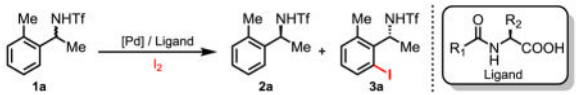
Table 1

Optimization of enantioselective C–H iodination.



entry	ligand		conv. (%)*	ee†		s‡
	R_1	R_2		2a	3a	
1	C_6H_5	^{n}Pr	38	50	83	17.6
2	C_6H_5	^{n}Bu	48	77	83	24.8
3	**C_6H_5**	**^{i}Bu**	**49**	**86**	**88**	**50**
4	C_6H_5	neopentyl	33	31	63	5.9
5	C_6H_5	^{i}Pr	48	79	87	30.8
6	C_6H_5	^{t}Bu	25	23	70	6.8
7	2-$CF_3C_6H_4$	^{i}Bu	48	80	88	34.2
8	3,5-$(CF_3)_2C_6H_3$	^{i}Bu	45	39	47	4.1
9	4-$OMeC_6H_4$	^{i}Bu	57	90	73	15.5
10	4-FC_6H_4	^{i}Bu	46	70	83	21.2
11	1-naphthyl	^{i}Bu	39	50	81	13.3
12	2-naphthyl	^{i}Bu	47	77	88	32.9
13	Me	^{i}Bu	24	15	48	3.2
14	CF_3	^{i}Bu	5	1	21	1.5
15	^{t}BuO	^{i}Bu	38	24	39	2.9
16§	C_6H_5	^{i}Bu	50	89	90	62.0
17‖	**C_6H_5**	**^{i}Bu**	**50 (50¶)**	**92 (89¶)**	**92 (89¶)**	**78.8 (51.2¶)**

Reaction conditions: 10 mol% $Pd(OAc)_2$, 40 mol% Ligand, 3 eq. Na_2CO_3, 3 eq. CsOAc, 3 eq. I_2, 15 eq. DMSO, 1mL ^{t}amyl-OH, air, 20 °C, 24 h

*Calculated conversion, c = **ee2a**/(**ee2a** + **ee3a**).

†Determined by chiral HPLC analysis.

‡Selectivity(s) = (rate of fast-reacting enantiomer)/(rate of slow-reacting enantiomer).

[§] 0.5 mL $t$amyl-OH.

[||] 0.5 mL $t$amyl-OH/DMSO (5 : 2.2).

[¶] Reaction conditions: 2 mol% $Pd(OAc)_2$, 10 mol% Bz-Leu-OH, 3 equiv. CsOAc, 3 equiv. Na_2CO_3, 3 equiv. I_2, 0.5 mL $t$amyl-OH/DMSO (5 : 2.2), air, 20 °C, 24 h, then 3 equiv. I_2, 20 °C, 24 h.

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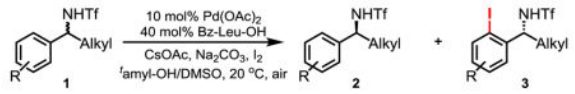
Table 2

Substrate scope of the enantioselective C–H iodination.

A

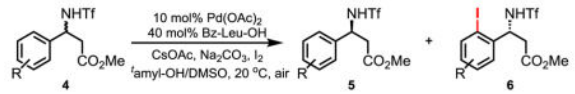


entry	1	Ar	Alkyl	time (h)	conv.* (yield, %)†	ee (%)‡		s§
						2	3	
1	**1a**	2-Me-Ph	Me	24	51 (48)	93	91	73.6
2	**1b**	2-Me-Ph	Et	24	50 (49)	91	91	67.3
3	**1c**	2-Me-Ph	^{n}Bu	48	47 (45)	77	87	32.9
4	**1d**	2-Me-Ph	^{i}Bu	48	51 (49)	83	81	25.0
5	**1e**	2-Me-Ph	Bn	48	47 (44)	67	75	13.8
6	**1f**	2-Me-Ph	cyclopropyl	24	42 (42)	70	95	83.5
7	**1g**	2-OMe-Ph	Me	24	49 (46)	93	97	240
8	**1h**	2-F-Ph	Me	24	48 (47)	89	96	148
9	**1i**	2-Me,4-Cl-Ph	Me	24	51 (49)	97	93	113
10	**1j**	3-Me-Ph	Me	24	45‖ (42, mono:di=3:1)	78	92¶	99.5
11	**1k**	4-Me-Ph	Me	48	45 (35)	78	95	91.7
12	**1l**	2-naphthyl	Me	48	41 (37)	67	95	76.0
13#	**1m**	Ph	^{n}Bu	48	42‖ (40, mono:di=1:1.4)	70	87¶ (99**)	124

B

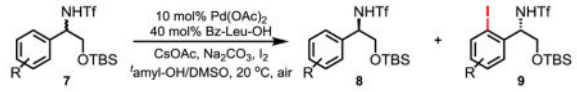
entry	4	Ar	time (h)	conv. (yield, %)	ee (%)		s
					5	6	
1	**4a**	Ph	48	47* (44, mono:di=2:1)	85	96‡	128
2	**4b**	2-Me-Ph	24	49 (49)	93	96	168

B



entry	4	Ar	time (h)	conv. (yield, %)	ee (%) 5	ee (%) 6	*s*
3	**4c**	3-Me-Ph	48	50 (44)	93	94	112
4	**4d**	4-OMe-Ph	48	46* (43, mono:di=3:1)	82	98‡	134
5†	**4e**	4-F-Ph	48	48 (41)	90	98	244
6†	**4f**	4-Cl-Ph	48	49 (40)	92	97	152
7†	**4g**	4-CF_3-Ph	48	40 (38)	65	99	155

C



entry	7	Ar	time (h)	conv. (yield, %)	ee (%) 8	ee (%) 9	*s*
1	**7a**	Ph	48	43* (40, mono:di=1:1)	71	87† (99‡)	88.0
2	**7b**	2-Me-Ph	48	50 (49)	91	92	77.2
3	**7c**	2-F-Ph	48	41 (41)	68	99	188
4	**7d**	2-naphthyl	48	43 (40)	72	96	112

*Calculated conversion, c = $\mathbf{ee_2}/(\mathbf{ee_2} + \mathbf{ee_3})$.

†Isolated yield of the iodinated product.

‡Determined by chiral HPLC analysis.

§Selectivity(*s*) = (rate of fast-reacting enantiomer)/(rate of slow-reacting enantiomer).

||Determined by crude ^{1}H-NMR.

¶ee for the mono product.

#3 equiv. I_2 was added after 24 h.

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** ee for the di product.

* Determined by crude ^{1}H-NMR.

† 3 equiv. I_2 was added after 24 h.

‡ ee for the mono product.

* Determined by crude ^{1}H-NMR.

† ee for the mono product.

‡ ee for the di product.