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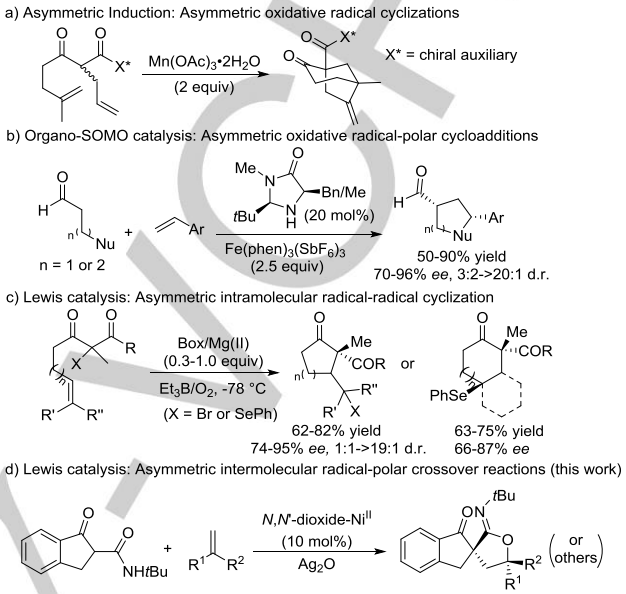
Enantioselective Radical-Polar Crossover Reactions of Indanonecarboxamides with Alkenes

Xiying Zhang, Wangbin Wu, Weidi Cao, Han Yu, Xi Xu, Xiaohua Liu,* Xiaoming Feng*

Abstract: Highly efficient asymmetric intermolecular radical-polar crossover reactions were realized by combining a chiral *N*,*N*′-dioxide-Ni^{II} complex catalyst with Ag_2O under mild reaction condition. Various terminal alkenes and indanonecarboxamides/ester underwent radical addition/cyclization reactions to afford spiroiminolactones and spirolactone with good to excellent yields (up to 99%) and enantioselectivities (up to 96% *ee*). Furthermore, a range of different radical-mediated oxidation/elimination or epoxide ring-opening products were obtained under mild reaction condition. The Lewis acid catalysts exhibited excellent excellent and kept down the strong background reaction.

The transformation of carbonyl moiety is of great significance in organic synthesis. Enantioselective α-nucleophilic addition of aldehydes or ketones has been extensively studied over the last two decades. Recently, the development of radical-initiated reactions upon the use of single electron transfer (SET) oxidation[1] to generate electrophilic α-carbonyl radicals remarkably enriches the chemistry of carbonyl compounds. For instance, the radical cyclization of carbonyl compounds with alkenes provides an efficient method for the synthesis of various cyclic arrays[2] which benefits modern drug design and screening. The seminal works of asymmetric oxidative radical cyclizations were achieved by Snider, Zoretic through introducing a chiral auxiliary (Scheme 1a).[3] Nevertheless, the control of stereoselectivity in such kind of catalytic asymmetric radical reaction is a great challenge, because it is hard to be further speeded up by chiral catalyst beyond strong, racemic backgroud reaction itself. Creative catalysts and strategies have been tailored to balance the reactivity and to modulate stereoseletivity in the processes.[4] One outstanding strategy is MacMillan's SOMO catalysis of alkyl aldehydes relied on the formation of enamine radical cation,[5] which has been successfully applied in asymmetric oxidative radical-polar cycloadditions of 3-arylpropanals and 3-aminopropanal with styrenes (Scheme 1b)[6] and others. Chiral Lewis acid catalysis has been used in enantioselective radical-involved reactions at the earliest. The pioneering work from Sibi's group and others focused on the complexation and activation of radical acceptors, such as α,β-unsaturated carbonyl compounds.[7] Alternatively, α-carbonyl radicals show enhanced reactivity upon complexation of the carbonyl oxygen atoms with a Lewis acid,[8] therefore it allows for control of the enantioselectivity via chiral Lewis acid activation of radical donors. The representative example is



Scheme 1. Asymmetric α-carbonyl radical transformations.

magnesium/bisoxazoline promoted asymmetric intramolecular radical-radical cyclization cascades from the Yang's group (Scheme 1c).[9] Another noteworthy report is related to SmI_2-mediated radical cyclization casdades, which is a different process that SET reduction of ketone generates nucleophilic ketyl radical anions for intramolecular cylcoaddition.[10] Even so, the discovery of efficient Lewis acid catalyst for enantioselective radical-initiated cycliazation remains to be an important and problematic issue in view of the scope of substrates, and the loading of chiral Lewis acids as well.

Radical-polar annulation of 1,3-dicarbonyl compounds with alkenes was demonstrated to be an efficient protocol to construct attractive heterocyclic skeletons.[11] For example, Youn and coworkers utilized a cooperative $In(OTf)_3/Ag_2O$ system to accelerate the reaction between 1,3-dicarbonyl compounds and styrenes, which yielded racemic five-membered heterocycles at high reaction temperature.[12] However, two point binding of radicals of 1,3-dicarbonyl compounds by the introducing of chiral Lewis acids is a promising strategy towards the enantioselective version of this radical cycliazation (Scheme 1d). Given the performance of chiral *N*,*N*′-dioxide-metal complexes in activation and stereocontrol of carbonyl compounds for polar additions and cyclization reactions via either single- or two-point binding,[13] we envision that with careful choice of this type of ligands and metal salts, the asymmetric catalytic radical-polar crossover reactions would be available under mild conditions. Herein, we presented chiral *N*,*N*′-dioxide-Ni^{II} complex for enantioselective radical-polar crossover reactions between indanonecarboxamides/ester and various terminal alkenes. The asymmetric radical-polar cyclization afforded spiroiminolactone and spirolactone products in good to excellent stereoselectivities. Meanwhile, other radical

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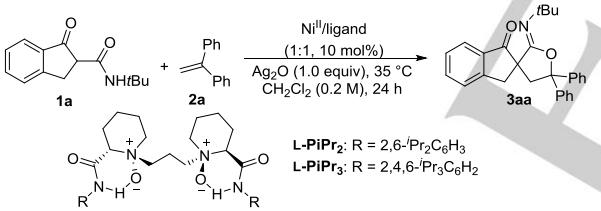
crossover reactions of different alkenes could yield a range of optically enriched coupling products, including alkene, aldehyde, ketone and alcohol, depending on the nature of the alkenes.

We began our study with the screening of the oxidants to generate the radical from indanonecarboxamide **1a**, which reacts with 1,1-diphenylethylene **2a** to perform radical addition/cyclization reaction. Chiral **L-PiPr$_2$**-Ni^{II} complex was used as the chiral Lewis acid catalyst in CH_2Cl_2 at 35 °C. It was found that Ag_2O was efficient to give the spiroiminolactone **3aa** in 84% yield with 90% *ee* (entry 1). Reducing the amounts of Ag_2O or utilizing cheaper oxidants instead, such as O_2, 2,3-dicyano-5,6-dichlorobenzoquinone (DDQ), $CuCl_2$ poor results were obtained (see SI for details). The counterions of nickel(II) salts had a significant effect on the enantioselectivity (entries 1-4, see SI for details). The reaction proceeded smoothly in the presence of $Ni(acac)_2$ or $NiCl_2$, but gave only racemic products. By contrast, $Ni(ClO_4)_2{\cdot}6H_2O$ could afford slightly higher enantioselectivity than $Ni(OTf)_2$ (entry 4; 93% *ee*). A possible reason is that coordinated counterions ($acac^-$, Cl^-) of the **L-PiPr$_2$**-Ni^{II} complexes are too strong to be exchanged by **1a**. When a more sterically encumbered ligand **L-PiPr$_3$** was used, **3aa** could be achieved with 95% *ee* and 76% yield (entry 5). Delightedly, the yield was raised to 86% with no loss of enantioselectivity by decreasing the concentration and increasing the amount of Ag_2O to 1.1 equivalents (entries 6-7). It was noteworthy that Ag_2O itself will undergo obvious racemic transformation without other catalytic speices, implying the competion of severe background reaction, which might partly enhance the difficulty in asymmetric control (entry 8).

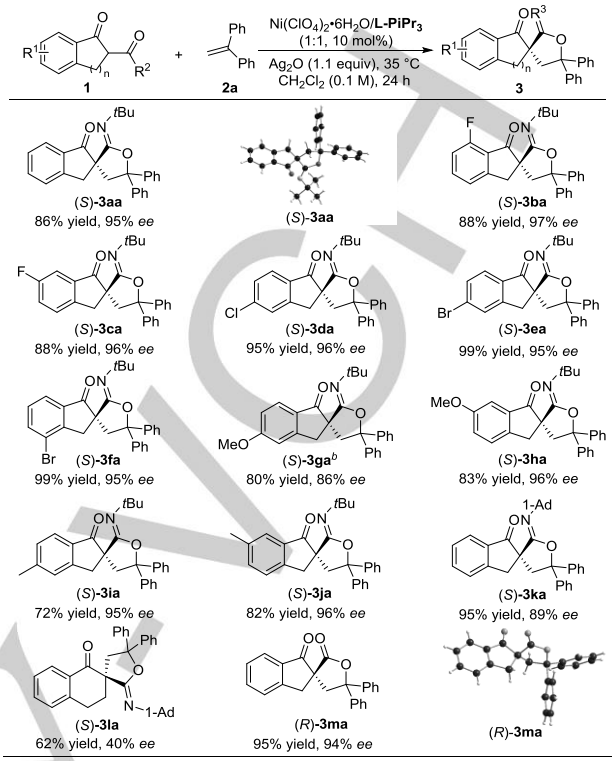
Table 1. Optimization of the reaction conditions



entry[a]	Ni^{II}	ligand	yield/%[b]	*ee*/%[c]
1	$Ni(OTf)_2$	**L-PiPr$_2$**	84	90
2	$Ni(acac)_2$	**L-PiPr$_2$**	68	0
3	$NiCl_2$	**L-PiPr$_2$**	92	0
4	$Ni(ClO_4)_2{\cdot}6H_2O$	**L-PiPr$_2$**	81	93
5	$Ni(ClO_4)_2{\cdot}6H_2O$	**L-PiPr$_3$**	76	95
6[d]	$Ni(ClO_4)_2{\cdot}6H_2O$	**L-PiPr$_3$**	82	94
7[d,e]	$Ni(ClO_4)_2{\cdot}6H_2O$	**L-PiPr$_3$**	86	95
8	-	-	99	0

[a] Unless otherwise noted, the reactions were performed with **1a** (0.10 mmol), **2a** (0.11 mmol), metal salt (10 mol%), ligand (10 mol%), oxidant (1.0 equiv) and CH_2Cl_2 (0.2 M) at 35 °C. [b] Isolated yields of **3aa**. [c] Determined by SFC on a chiral stationary phase. [d] CH_2Cl_2 (0.1 M). [e] Ag_2O (1.1 equiv). *t*Bu = tertiary butyl, Tf = trifluoromethanesulfonyl, acac = acetylacetonate. N.D. = no detection.

Table 2. Substrate scope of indanonecarboxamides/ester[a]

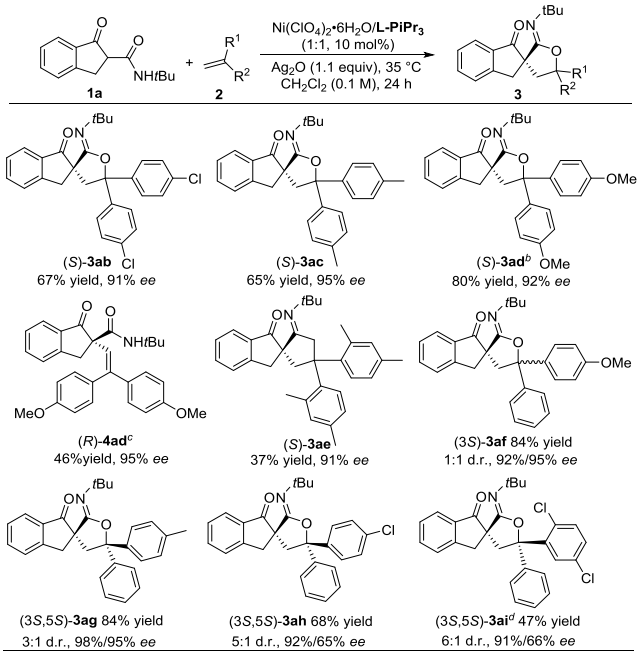


[a] Unless otherwise noted, the reactions were performed with **1** (0.10 mmol), **2a** (0.11 mmol), $Ni(ClO_4)_2{\cdot}6H_2O$ (10 mol%), **L-PiPr$_3$** (10 mol%), Ag_2O (1.1 equiv) and CH_2Cl_2 (0.1 M) at 35 °C. Isolated yields of **3**. The *ee* value was determined by SFC on a chiral stationary phase. [b] $Ni(OTf)_2$/**L-PiPr$_2$** as the catalyst. 1-Ad = 1-adamantyl.

The applicability of this catalytic system to a range of **1** with **2a** was shown in Table 2. Various indanonecarboxamides bearing different substituents on the aryl ring (**1a**-**1j**) were tolerated to provide the corresponding spirocyclic products (**3aa**-**3ja**)[14] with good to excellent enantioselectivities (86-97% *ee*). The substrate (**1k**) with hindered ester substituent could also give **3ka** with good result (95% yield and 89% *ee*). 1-Tetralone derivative **1l** was also probed, affording **3la** in 62% yield and 40% *ee* along with the byproduct naphthol via overoxidation of **1l**. Furthermore, the indanonecarboxester **1m** was applicable for the reaction as well, and gave the spirolactone **3ma** in 95% yield with 94% *ee*.[14] Unfortunately, the acyclic β-ketoamides couldn't give the corresponding products (see SI for details).

We next turned attention to the scope of terminal alkenes (Table 3). Firstly, 1,1-diarylethylenes were explored under the optimized reaction conditions. *p*-Cl-Substituted substrate **2b** and *p*-Me-substituted alkene **2c** were transformed into the desired products **3ab** and **3ac** in good yields and enantioselectivities (67% and 65% yield, 91% and 95% *ee*, respectively). For electron-rich bis-4-methoxyphenyl substituted ethylene **2d**, the products varied with the reaction temperature. The corresponding spiroiminolactone **3ad** was generated in 80% yield with 92% *ee* at a higher temperature (60 °C) in CH_2ClCH_2Cl. Nevertheless, formal alkenylation product **4ad** was isolated in 46% yield and 95% *ee* in $CHCl_2CHCl_2$ at 35 °C. Introducing *ortho*-substituents to aryl groups of 1,1-diarylethylene (**2e**) led to dramatically decreased yield of spiroiminolactone **3ae** (37%) due to the

Table 3. The substrate scope of terminal 1,1-diarylalkenes[a]



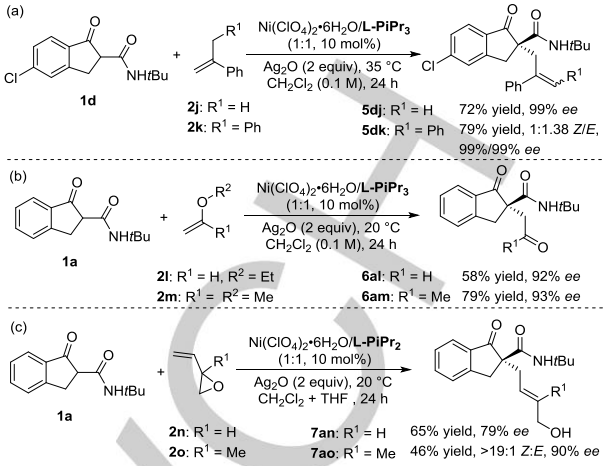
[a] As same as the footnote a in Table 2. [b] CH_2ClCH_2Cl (0.1 M) as solvent at 60 °C. [c] $CHCl_2CHCl_2$ (0.1 M). [d] The absolute configuration of the major isomer of **3ai** was determined to be (3*S*,5*S*) by X-ray crystallography.[14]

formation of some side products. When 1,1-diarylethylenes bearing a phenyl and a substituted aryl group were tested, enantio- and diastereoselective cyclization occurred (**3af**-**3ai**), and it revealed that the diastereoselectivity increased gradually from electron-rich aryl group to electron-deficient groups in the ethylenes.

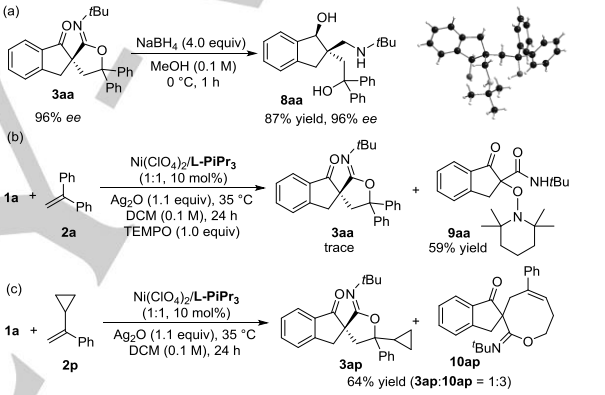
Subsequently, we extended the substrate scope to other types of alkenes (Scheme 2). For α-methyl substituted styrene **2j** and α-benzyl substituted styrene **2k**, they underwent an oxidative coupling then *β*-hydrogen elimination process instead of cyclization, yielding allyl cross-coupling products **5dj** and **5dk** with excellent enantioselectivities (Scheme 2a). When enol ethers **2l** and **2m** were used as the radical acceptor, they were transformed into **6al** and **6am** containing acetaldehyde or propanone substituent in good enantioselectivities and moderate yields (Scheme 2b). Gratifyingly, upon tuning the reaction conditions (see SI for detailed), 2-vinyloxirane **2n** and **2o** reacted with **1a** smoothly to give but-2-enol substituted products **7an** and **7ao** in 65% yield, 79% *ee* and 46% yield, >19:1 *Z*/*E*, 90% *ee,* respectively, after epoxide ring-opening (Scheme 2c).

To evaluate the synthetic potential of the catalytic system, a scale-up experiment was performed between **1a** (3.0 mmol) and **2a** (3.3 mmol) under the optimized reaction conditions, providing (*S*)-**3aa** in 62% yield with 94% *ee* (See SI for details). Upon treatment of **3aa** with $NaBH_4$ in MeOH, the reduction product amino alcohol **8aa**[14] was obtained with 87% yield and a maintained *ee* value (Scheme 3a).

We sought to establish the involvement of radical species in the process (see SI for details). If the equivalent amount of 2,2,6,6-tetramethylpiperidinooxy (TEMPO) was used as a radical trap under the optimized reactions, trace amount of the product **3aa** with the concurrent formation of TEMPO-trapped product



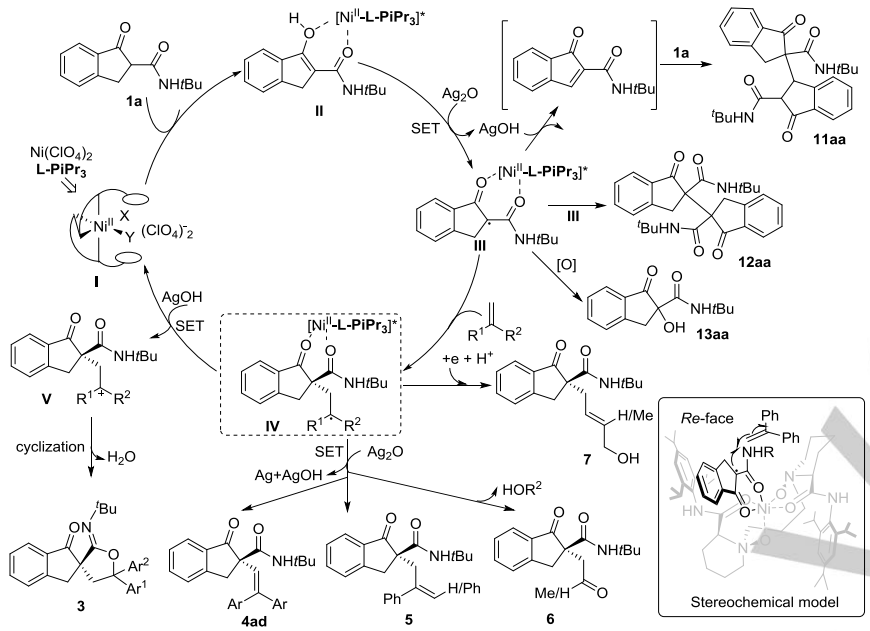
Scheme 2. Substrate scope of other substituted alkenes. THF = tetrahydrofuran



Scheme 3. The transformation of the product **3aa** and control experiments.

9aa (59% yield) were observed (Scheme 3b). Furthermore, the reaction of (1-cyclopropylvinyl)benzene **2p** which could act as a radical clock substrate, afforded the mixture of the related cyclization product **3ap** and ring-opening/cyclization product **10ap** in 64% yield (**3ap**:**10ap** = 1:3). These experiments support the intermediacy of radical species (Scheme 3c).

Based on above experimental results, we rationalized the possible catalytic process for the radical-polar crossover reactions. As illustrated in Scheme 4, the Lewis acid catalyst **I** *in situ* generated from the tetradentate **L-PiPr$_3$** and $Ni(ClO_4)_2{\cdot}6H_2O$, coordinates with **1a** to form the intermediate **II**, which subsequently undergoes a single electron oxidation in the presence of Ag_2O and affords the radical intermediate **III**. The complexed α-carbonyl radicals by the catalyst is more electrophilic, and then add to the electron-rich alkenes[15] rapidly and facial-preferentially. The formed radical **IV** is oxidized to the carbocation intermediate **V**, and subsequent intramolecular cyclization yields the spirocyclic product **3**. Meanwhile, some byproducts were detected in some cases, including **11aa** via oxidative elimination/Michael addition sequence, **12aa** via homocoupling and **13aa** via α-hydroxylation.[16] When alkenes with different substituents are involved, oxidative elimination occurs due to the stability of the radical species **IV**. Thus, radical



Scheme 4. The proposed mechanism.

crossover products, such as **4ad**, **5**, and **6** are generated as the major products. For the substrate of vinyl epoxides, the species undergoes radical epoxide-opening, SET reduction and proton abstract to give the allyl alcohols **7**.[17]

In conclusion, we have developed catalytic asymmetric intermolecular radical-polar crossover reactions between styrene derivatives and indanonecarboxamides/ester by combining a chiral *N*,*N*′-dioxide-Ni^{II} complex catalyst with Ag_2O. A wide range of chiral spirocycles containing a quaternary all-carbon stereocenter was obtained in excellent yields with good to excellent diastereo- and enantioselectivities. In addition, various alkenes delivered four special functionalized products (such as alkene, aldehyde, ketone, alcohol) with good outcomes. Further studies on stereoselective chemistry in radical reactions are underway.

Acknowledgements

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Keywords: asymmetric catalysis • alkenes • chiral Lewis acid • oxidation • radical-polar crossover reaction

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[14] CCDC 1936920 (**3aa**), 1936920 (**3ma**), 1945357 (**3ai**) and 1939349 (**8aa**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[15] The 1,1-diarylethylenes are easily oxidized to the diarylketones with the presence of Ag_2O, which leads to the reaction be more challenging.

[16] In the absence of olefins **2** or with low reactivity of ethylenes **2**, which did not undergo the desired transformation, product **11aa** was obtained as the major product. The product **12aa** was obtained by using $CuCl_2$ (2 equiv) instead of Ag_2O as the oxidant. See Supporting Information for details

[17] J. He, J. Ling, P. Chiu, *Chem. Rev.* **2014**, *114*, 8037.

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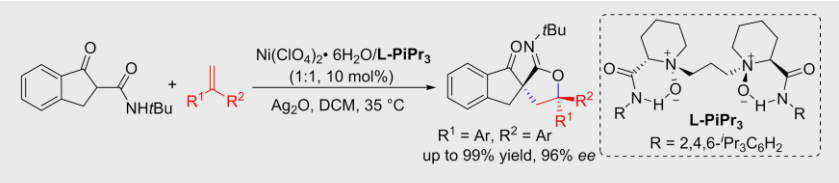

A highly efficient asymmetric radical-polar crossover reaction of Indanonecarboxamides/ester and various electron-rich alkenes was realized by combining a chiral *N*,*N*′-dioxide-Ni^{II} complex catalyst with Ag_2O. Five types of products could be obtained with good to excellent yields and *ee* values.

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