Double Functionalization of *N*-Boc-3-(Tosylmethyl)indole Exploiting the Activating Properties of the Tosyl Group

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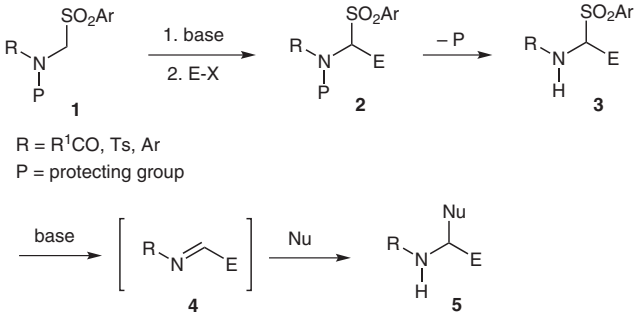
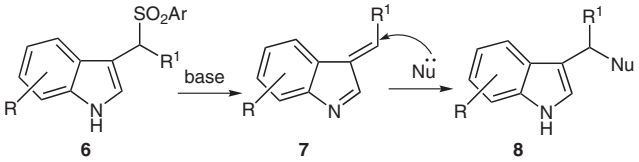
Abstract: The anion prepared from *N*-Boc-3-(tosylmethyl)indole using NaH in DMF can be readily functionalized by reaction with various electrophiles. The obtained sulfonyl indoles, upon removal of the N-protecting group, undergo nucleophilic attack via a vinylogous imino derivative, leading to branched 3-substituted indoles.

Key words: carbanions, eliminations, indoles, nucleophilic additions, sulfones

The sulfonyl group is widely recognized as an important activating moiety for the assembly of various structural entities through carbon–carbon bond formation.[1] Stabilization of carbanionic species at α-position of sulfonyl derivatives provides an enolate-like reagent that is able to react with various electrophilic systems.[2] After this synthetic operation, the sulfonyl group is usually removed since it is hardly found in targets of practical interest.[3] The latter operation is often carried out by a reductive process that entails substitution of the sulfonyl group with a hydrogen atom.[4] Alternatively, as in the Julia reaction, the β-acyloxysulfone produced by condensation of sulfonyl carbanions with aldehydes and subsequent acylation is reductively converted into an olefin.[5] The above cited procedures aimed to the removal of the sulfonyl group do not introduce any significant structural modification into the resulting molecule. From a synthetic standpoint reductive alkylations and nucleophilic displacement of the sulfonyl group represent a more appealing process that involves implementation of the molecular carbon backbone. Reductive alkylations are rather limited in scope while nucleophilic displacement of the sulfonyl group is particularly effective on allyl and vinylsulfonyl derivatives by means of an addition–elimination process.[6] An opposite pattern is usually observed when α-alkoxy or α-amido sulfones are involved in such reactions since in this instance, elimination of the sulfonyl group must precede the nucleophilic addition.[7] The nature of the intermediate observed after the elimination step is very likely an oxonium or an iminium ion working under acidic (mostly Lewis) conditions but *N*-acylimines[8] are certainly involved operating under basic conditions with α-amido sulfones. Coupling the anionic stabilization properties of the sulfonyl group with its ability to act as good leaving group in elimination reactions it is possible to devise an overall synthetic strategy as depicted in Scheme 1.[9] Sulfone **1** can be alkylated leading to compound **2** via the corresponding stabilized carbanion and after removal of the N-protecting group and transformation into the amino derivative **3**. Base-induced elimination of arenesulfinic acid from **3** produces the intermediate imino derivative **4** which upon nucleophilic addition affords difunctionalized amino compound **5**. This synthetic strategy can be also applied to vinylogous imino derivatives provided that an efficient entry to their precursors is achievable.



Scheme 1



Scheme 2

Recently, we have demonstrated that 3-(1-arylsulfonylalkyl)indoles **6** are able to eliminate arenesulfinic acid under basic condition leading to reactive intermediates **7** that closely resemble vinylogous imino derivatives which upon nucleophilic addition afford the corresponding 1′-substituted indoles **8** (Scheme 2).[10]

In this context sulfonyl indoles **6** represent a valid alternative to the utilization of gramines (*N*,*N*-dialkyl-3-indolylmethanamines) that, in order to generate the intermediate vinylogous imine **7**, require harsh reaction conditions.[11] The overall process allows a functional group implementation on 3-substituted indoles and complements direct functionalization of indoles using strong electrophilic reagents, a process widely known as the Friedel–Crafts reaction.[12] Introduction of suitable frameworks in the indole nucleus constitutes a gateway for the preparation of indole-based biologically active compounds.[13] The effec-

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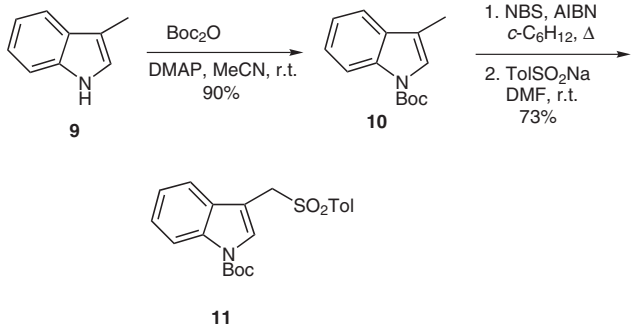
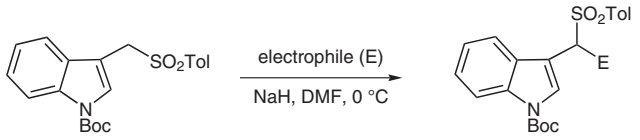


Scheme 3

tiveness of sulfonyl indoles **6** for this purpose have been proved in the reaction with stabilized carbanions, Grignard and Reformatsky reagents as well as in different reductive removals of the arenesulfonyl group. In order to evaluate the viability of the overall synthetic plan portrayed in Scheme 1 we decided to prepare *N*-Boc 3-(tosylmethyl)indole (**11**) starting from 3-methyl indole **9** that upon protection gives the corresponding *N*-Boc derivative **10** (Scheme 3).[14] Radical bromination of indole **10** followed by nucleophilic displacement by sodium *p*-toluenesulfinate finally leads to compound **11** in satisfactory overall yield.[15]

Generally, α-sulfonyl anions are generated by reaction of the corresponding sulfones with *n*-BuLi or LDA in ethereal solvents. However, we observed that NaH in DMF at 0 °C is effective in converting sulfonyl indole **11** into the corresponding anion which can be subsequently made to react with a wide range of electrophilic reagents leading to the corresponding adducts **12** (Table 1).[16] Simple allylation of sulfonyl indole **11** is possible using allyl bromide which is more effective than the corresponding sulfonate in producing compound **12a** (Table 1, entries 1 and 2). Other functionalized allyl halides tested for this process also provide satisfactory yields in this reaction. Particularly, a considerable α-regioselectivity is observed in the reaction of indole **11** with some substituted allyl chlorides (Table 1, entries 3–5). The introduction of an alkynyl group is efficiently achieved by reaction of **11** with propargyl chloride leading to indole **12f** (Table 1, entry 7). Benzyl bromides are the most effective electrophiles in the reaction with the sulfonyl anion generated from compound **11**, although simple alkyl iodides such as butyl iodide and 1-chloro-4-iodobutane give satisfactory results in the same process (Table 1, entries 10 and 11). The utilization of reactive halides is instrumental for an efficient reaction as demonstrated for the chemoselective nucleophilic substitution of 1-chloro-4-iodobutane and the modest results obtained with 5-bromopent-1-ene (Table 1, entry 12). Interestingly, 3-bromopropanenitrile gives better results compared to 5-bromopent-1-ene (Table 1, entry 13). This outcome can be probably ascribed to a preliminary base-assisted elimination of HBr from 3-bromopropanenitrile generating acrylonitrile which undergoes conjugate addition with the anion of compound **11**. As a matter of fact, acrylonitrile itself is able to provide the same result when directly employed in this reaction (Table 1, entry 14). Finally, conjugate addition to methyl acrylate and phenylvinyl sulfone demonstrates that compound **11** can be efficiently employed in Michael additions with electron-poor olefins as well (Table 1, entries 15 and 16).

Table 1 Reaction of Sulfonyl Indole **11** with Electrophiles in the Presence of NaH in DMF



11 **12**

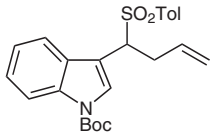
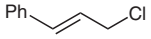
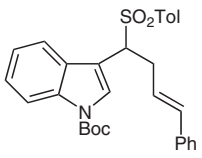
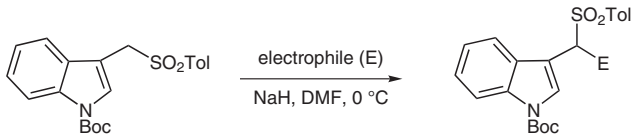
Entry	Electrophile	Product	Time (h)	Yield (%)[a]
1		 **12a**	2	70
2		**12a**	6	53
3		 **12b**	1	74

Table 1 Reaction of Sulfonyl Indole **11** with Electrophiles in the Presence of NaH in DMF (continued)



11 **12**

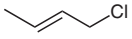
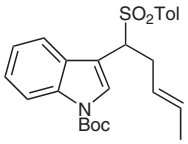
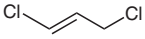
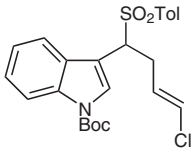
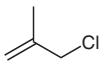
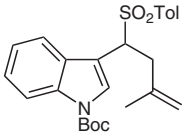
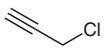
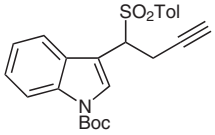
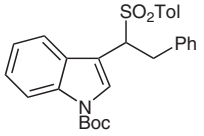
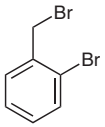
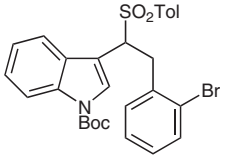
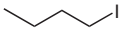
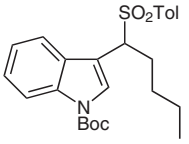
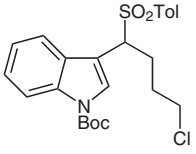
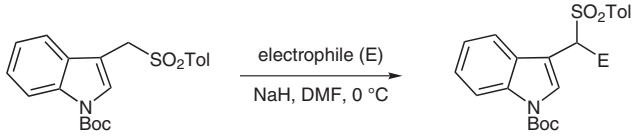
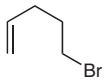
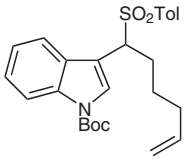
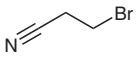
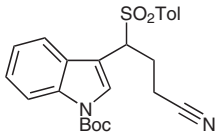
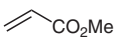
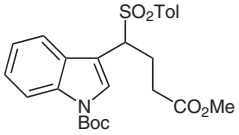
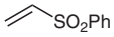
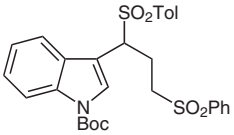
Entry	Electrophile	Product	Time (h)	Yield (%)[a]
4		 **12c**	4	54
5		 **12d**	4	60
6		 **12e**	4	61
7		 **12f**	4	72
8		 **12g**	2	84
9		 **12h**	3	88
10		 **12i**	2	80
11		 **12j**	2	65

Table 1 Reaction of Sulfonyl Indole **11** with Electrophiles in the Presence of NaH in DMF (continued)



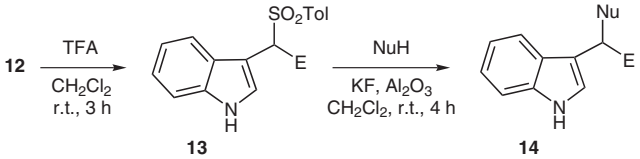
11 **12**

Entry	Electrophile	Product	Time (h)	Yield (%)[a]
12		 **12k**	14	52
13		 **12l**	3	70
14		**12l**	3	63
15		 **12m**	1	77
16		 **12n**	1	64

[a] Yields of pure, isolated products.

Sulfonyl indoles **12** prepared by this alkylative process can be fruitfully used in a subsequent process involving a base-promoted elimination of arenesulfinic acid followed by nucleophilic addition to the resulting vinylogous imino derivative.[10c] Thus removal of the *N*-Boc protecting group from compounds **12**[17] affords the corresponding sulfonyl indoles **13** that, following our synthetic protocol, react with various methylene active compounds in the presence of KF and basic alumina leading to 3-substituted indoles **14** in satisfactory yields (Table 2).[18]

Table 2 Deprotection of Sulfonyl Indoles **12** and Reaction with Methylene Active Compounds in the Presence of KF and Basic Alumina



13 **14**

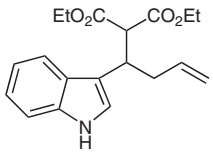
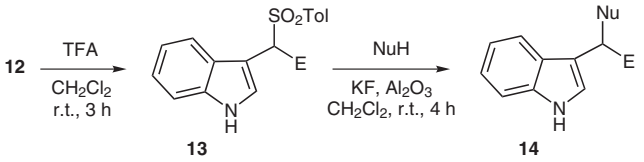
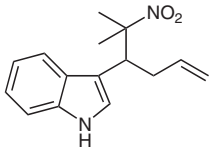
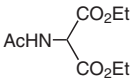
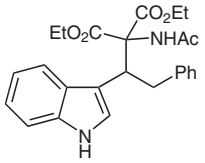
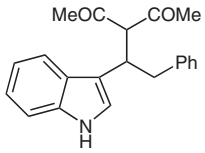
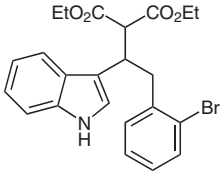
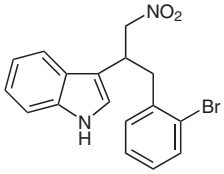
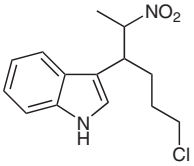
Entry	Indole	Yield of **13** (%)[a]	Nucleophile	Product	Yield of **14** (%)[a]
1	**12a**	89		 **14a**	75

Table 2 Deprotection of Sulfonyl Indoles **12** and Reaction with Methylene Active Compounds in the Presence of KF and Basic Alumina (continued)



Entry	Indole	Yield of **13** (%)[a]	Nucleophile	Product	Yield of **14** (%)[a]
2	**12a**	90		 **14b**	76
3	**12g**	86		 **14c**	83
4	**12g**	87		 **14g**	64
5	**12h**	86		 **14e**	74
6	**12h**	85	$MeNO_2$	 **14f**	66
7	**12j**	81	$EtNO_2$	 **14g**	77

[a] Yields of pure, isolated products.

The mild basic conditions required for the elimination–addition process on sulfonyl indoles **13** do not promote any double-bond isomerization of compounds **14a**,**b** (Table 2, entries 1 and 2). Furthermore, the poor reactivity shown by nitroalkanes toward C-alkylation allows a chemoselective addition of nitroethane on sulfonyl indole obtained by deprotection of **12j** leading to compound **14g** (Table 2, entry 7). Compound **14c**, obtained by reaction with diethyl 2-(acetylamino) malonate, is particularly interesting since its hydrolysis and decarboxylation provides a straightforward entry to tryptophan analogues.[19]

In conclusion, the tosyl group in *N*-Boc-3-(tosylmethyl)indole (**11**) assists deprotonation at α-position allowing an easy reaction of the corresponding carbanion with different electrophilic reagents. Subsequently, the aptitude of the tosyl group in acting as a good leaving group in

elimination processes can be utilized to generate a vinylogous imino derivative, which can be made to react with stabilized carbanions. The overall strategy represents a new example of umpoled synthon, which can be profitably used to prepare branched 3-substituted indoles bearing different functional groups.

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(15) **Synthesis of *N*-Boc-3-(Tosylmethyl) indole (11)**
To a solution of *N*-Boc-3-(bromomethyl) indole (5 mmol, 1.55 g) in DMF (10 mL), Bu_4NI (0.5 mmol, 0.18 g) and $TolSO_2Na$ were added at r.t. After stiring for 2 h at this temperature, cold H_2O (30 mL) was added and the mixture was extracted with EtOAc (3 × 30 mL). The organic phase was dried over $MgSO_4$, and after removal of the solvent the residue was purified by column chromatography (hexanes–EtOAc, 8:2) giving 1.54 g (80% yield) of pure **11** as a white solid; mp 124–126 °C. IR (Nujol): 1374, 1151 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.63 (s, 9 H), 2.37 (s, 3 H), 4.42 (s, 2 H), 7.08–7.12 (m, 1 H), 7.19 (d, 2 H, *J* = 10.7 Hz), 7.21–7.28 (m, 2 H), 7.45 (s, 1 H), 7.59 (d, 2 H, *J* = 8.5 Hz), 8.09 (d, 1 H, *J* = 8.1). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 28.2, 54.0, 84.3, 107.9, 115.2, 119.0, 122.9, 124.8, 126.2, 127.4, 128.7, 129.7,135.2, 136.7, 144.9, 149.8.
(16) **Reaction of *N*-Boc-3-(Tosylmethyl) indole (11) with Electrophiles**
To a mixture of NaH (2 mmol) in anhyd DMF (5 mL), sulfonyl indole **11** (1 mmol) was added at 0 °C. After 20 min stirring at this temperature, the electrophile (1.1 mmol) was added and stirring was continued for the appropriate time at 0 °C (see Table 1). The mixture was then cautiously quenched by addition of cold H_2O and then acidified with AcOH. After extraction with Et_2O (3 × 15 mL) the organic phase was dried over $MgSO_4$ and after removal of the solvent the residue was purified by column chromatography (hexanes–EtOAc, 8:2).
Spectroscopic Data for Representative Compounds
Compound **12a**: mp 58–60 °C. IR (Nujol): 1598, 1370, 1155 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.67 (s, 9 H), 2.35 (s, 3 H), 2.83–3.06 (m, 1 H), 3.10–3.28 (m, 1 H), 4.39 (dd, 1 H, *J* = 4.0, 11.4 Hz), 4.92–5.12 (m, 2 H), 5.52–5.75 (m, 1 H), 7.05–7.21 (m, 3 H), 7.23–7.37 (m, 2 H), 7.44–7.60 (m, 3 H), 8.09 (d, 1 H, *J* = 8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8, 28.4, 32.6. 63.4, 84.5, 112.2, 115.3, 118.6, 119.4, 122.9, 124.8, 126.7, 129.4, 129.6, 133.3, 134.4, 135.3, 144.9, 149.5.
Compound **12f**: mp 55–57 °C. IR (Nujol): 3310, 2133, 1368, 1151 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.67 (s, 9 H), 1.85 (s, 1 H), 2.36 (s, 3 H), 3.04–3.11 (m, 1 H), 3.27–3.32 (m, 1 H), 4.56 (dd, 1 H, *J* = 4.1, 10.7 Hz), 7.10–7.17 (m, 3 H), 7.20–7.27 (m, 2 H), 7.52–7.62 (m, 3 H), 8.10 (d, 1 H, *J* = 8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5, 21.8, 28.4, 62.2, 71.3, 79.3, 84.6, 115.4, 119.3, 123.0, 124.9, 126.7, 129.4, 129.5, 129.6, 129.8, 133.9, 135.2, 145.3, 149.5.
Compound **12l**: mp 56–58 °C. IR (Nujol): 2248, 1376, 1153 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.67 (s, 9 H), 2.35 (s, 3 H), 2.46–2.62 (m, 2 H), 2.80–2.96 (m, 2 H), 4.46 (dd, 1 H, *J* = 4.7, 10.7 Hz), 7.12–7.18 (m, 3 H), 7.26–7.38 (m, 2 H), 7.51–7.60 (m, 3 H), 8.10 (d, 1 H, *J* = 8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.5, 21.7, 24.7, 28.3, 62.3, 84.9, 110.5, 115.5, 118.3, 119.3, 123.3, 125.2, 126.7, 129.3, 129.8, 134.1, 137.8, 145.3, 149.7.
Compound **12m**: mp 52–54 °C. IR (Nujol): 1742, 1374, 1156 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.66 (s, 9 H), 2.34 (s, 3 H), 2.36–2.49 (m, 2 H), 2.67–2.78 (m, 2 H), 3.58 (s, 3 H), 4.52 (dd, 1 H, *J* = 4.3, 10.7 Hz), 7.10–7.20 (m, 3 H), 7.22–7.34 (m, 2 H), 7.48 (s, 1 H), 7.55 (d, 2 H, *J* = 8.1 Hz), 8.09 (d, 1 H, *J* = 8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 24.1, 28.3, 31.1, 51.8, 62.5, 84.6, 111.9, 115.4, 119.4, 123.0, 125.0, 126.6, 129.3, 129.6, 134.5, 135.4, 144.9, 149.8, 172.8.
(17) The free NH on the indole ring is mandatory for a successful process since none of the nucleophilic reagents tested in this reaction gives any result with *N*-Boc indoles **12**.
(18) **Deprotection of *N*-Boc Sulfonyl Indoles 12 and Their Reaction with Nucleophiles**
N-Boc indole **12** (1 mmol) was dissolved in a mixture of TFA–CH_2Cl_2 (1:1, 10 mL) and stirring was continued for 3 h at r.t. After evaporation of the solvents at reduced pressure, the crude sulfonyl indole was purified by column chromatography (hexanes–EtOAc, 8:2). Reaction of sulfonyl indoles **13** with nucleophiles was carried out according to our previously published procedure (ref. 10c).

Spectroscopic Data for Representative Compounds

Compound **14a**: oil. IR (neat): 3393, 1739, 1603, 1463 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, 2.3 H, *J* = 7.3 Hz), 1.27 (t, 2.5 H, *J* = 6.8 Hz), 1.28 (t, 1.2 H, *J* = 7.3 Hz), 2.55–2.69 (m, 2 H), 3.84–3.92 (m, 3 H), 4.16–4.28 (m, 3 H), 4.87–4.99 (m, 2 H), 5.61–5.68 (m, 1 H), 7.02 (d, 1 H, *J* = 2.1 Hz), 7.08–7.18 (m, 2 H), 7.31 (d, 1 H, *J* = 7.7 Hz), 7.66 (d, 1 H, *J* = 7.7 Hz), 8.24 (br s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 14.3, 37.0, 38.0, 57.6, 57.6, 61.4, 61.7, 111.4, 115.2, 116.9, 119.5, 119.6, 122.1, 122.8, 127.0, 136.1, 136.4, 168.6, 168.9.

Compound **14b**: oil. IR (neat): 3389, 1622, 1583, 1458 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.51 (s, 3 H), 1.65 (s, 3 H), 2.33–2.39 (m, 1 H), 2.59–2.68 (m, 1 H), 3.82 (dd, 1 H, *J* = 3.4, 11.5 Hz), 4.80 (d, 1 H, *J* = 9.9 Hz), 4.95 (dd, 1 H, *J* = 1.3, 17.1 Hz), 5.48–5.55 (m, 1 H), 7.04 (d, 1 H, *J* = 2.6 Hz), 7.13–7.23 (m, 2 H), 7.37 (d, 1 H, *J* = 8.1 Hz), 7.68 (d, 1 H, *J* = 7.7 Hz), 8.19 (br s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8, 26.8, 34.9, 45.7, 93.0, 111.5, 113.3, 116.7, 119.7, 120.1, 122.4, 123.4, 128.3, 136.1, 136.2.

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