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FULL PAPER

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Hydroxylamine-*O*-Sulfonic Acid (HOSA) as a Redox–Neutral Directing Group: Rhodium Catalyzed, Additive Free, One-Pot Synthesis of Isoquinolines from Arylketones

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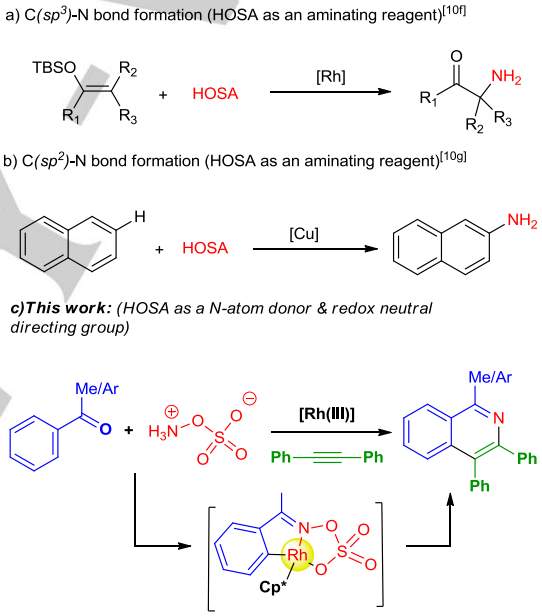
Abstract: A new application of hydroxylamine-*O*-sulfonic acid (HOSA) has been discovered whereby aromatic ketones react with HOSA and alkynes to form isoquinolines in the presence of a Rh(III) catalyst. This C-H/N-O annulation methodology gives excellent yields even without any silver additive, acid/base or metal oxidant. This is the first report wherein a directing group is simultaneously forming in situ, acting as acid additive, and also as an internal oxidant.

Introduction

Compared with traditional methods, transition metal-catalyzed C-H bond activation with subsequent functionalization represents a more direct strategy for the synthesis of pharmaceutically important heterocycles, including quinolines and isoquinolines.[1] C-H bond activation has advantages in terms of more concise synthetic routes. Nevertheless, some drawbacks may be encountered, including the use of stoichiometric heavy metal oxidants, covalently attached directing groups which must later be removed and use of acid or base additives.[2] Hence, there is a need to develop more general and straightforward methods of C-H bond activation in heterocycle synthesis.

Discovering a new directing group, which can serve as an effective ligand and in some cases, oxidant, but also balance the required reactivity with selectivity, is a challenging task.[3] The Fagnou[4] and Glorius[5] groups have made considerable progress in the development of redox-neutral directing groups (no use of heavy metal oxidant) for the oxidative C-H/N-O annulation of alkynes using Cp*Rh(III) complexes to access isoquinoline/isoquinolone derivatives. Glorius, Sundararaju, Chiba, Jeganmohan and several other groups independently have explored different types of redox neutral directing groups towards the construction of azaheterocycles.[6] However they still needed to use extra acid/base additive and one extra step required to install the directing group. In recent years, developing an in situ/transient directing group is gaining prominence due to step economy. Yu and other groups have explored this in situ/transient directing group concept in the Pd(II)-catalyzed C-H functionalization by using amino acids as directing group, however they still needed to use extra acid additive and metal oxidant.[7] Invariably for C-H functionalization reactions involving transient directing groups, acid additives were commonly used to drive the substrate-directing group binding equilibrium.[7] In C-H activation reactions it has been observed that, additional acid or base additives are showing positive cooperativities either as a ligand for the cyclometalated intermediate or by making active catalyst within the reaction condition.[8] Therefore, discovery of a directing group is highly needed which can simultaneously act as in situ traceless directing group, substitute for acid additive as well as internal oxidant whereby solving all the three issues viz. (1) step economy (2) use of acid additive and (3) use of heavy metal oxidant.[9]

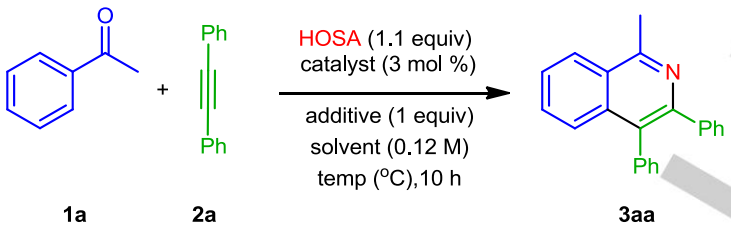


Scheme 1. Comparison with previous work.

Hydroxylamine-*O*-sulfonic acid (HOSA) may correspond to either an electrophilic (NH^{2+} synthon) or a nucleophilic (NH^{2-} synthon) reagent depending on the substrates and reaction conditions adopted.[10] Recently, HOSA has been used as C-H aminating agent for naphthalenes and silyl enol ethers in the presence of transition metal catalyst (Scheme 1, a-b).[10f, g]

Intrigued by the experimental and computational studies by Chen group on the importance of neutral and anionic bidentate ligands as well as weakly coordinating directing groups[11] and above-mentioned challenges, we hypothesized that HOSA might act as a new redox-neutral directing group for C-H activation. Most importantly inherent mild acidity of HOSA might help for in situ imination and C-H activation (Scheme 1, c).

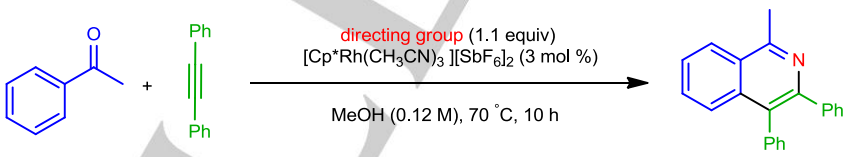
Table 1. Optimization studies.[a],[b]



1a **2a** **3aa**

Entry	Solvent	Catalyst	Additive	Temp (°C)	Yield [%][c]
1	MeOH	$[Cp^*RhCl_2]_2$	KOAc	100	30
2	HFIP	$[Cp^*RhCl_2]_2$	KOAc	100	nr[d]
3	Toluene	$[Cp^*RhCl_2]_2$	KOAc	100	nr[d]
4	MeOH	$[Cp^*RhCl_2]_2$	NaOAc	100	nr[d]
5	MeOH	$[Cp^*RhCl_2]_2$	LiOAc	100	13
6	MeOH	$[Cp^*RhCl_2]_2$	CsOAc	100	61
7	MeOH	$[Cp^*CoI_2]$	CsOAc	100	nr[d]
8	MeOH	$Co(acac)_2$	CsOAc	100	nr[d]
9	MeOH	$Co(acac)_3$	CsOAc	100	nr[d]
10	MeOH	$[RuCl_2\ (p\text{-cymene})]_2$	CsOAc	100	nr[d]
11	MeOH	$[Cp^*RhL_3][SbF_6]_2$	CsOAc	100	80
12	MeOH	$[Cp^*RhL_3][SbF_6]_2$	-	100	90
13	MeOH	$[Cp^*RhL_3][SbF_6]_2$	-	60	63
14	MeOH	$[Cp^*RhL_3][SbF_6]_2$	-	70	92
15	MeOH	$[Cp^*RhL_3][SbF_6]_2$	-	80	89

[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.13 mmol), HOSA (0.11 mmol), Cp*Rh (3 mol %), additive (1 equiv), solvent (0.12 M), temp (°C), 10 h. L = CH_3CN. [b] See the supporting information for details. [c] NMR yields using 1, 3, 5-trimethoxybenzene as an internal standard. [d] No reaction.



1a **2a** **3aa**

Directing group	$H_2NOH.HCl$	$H_2NOMe.HCl$	NH_4OAc	$H_2N\text{-}NH\text{-}CO_2{}^tBu$	HOSA
Isolated Yield	nd	nd	21%	nd	89%

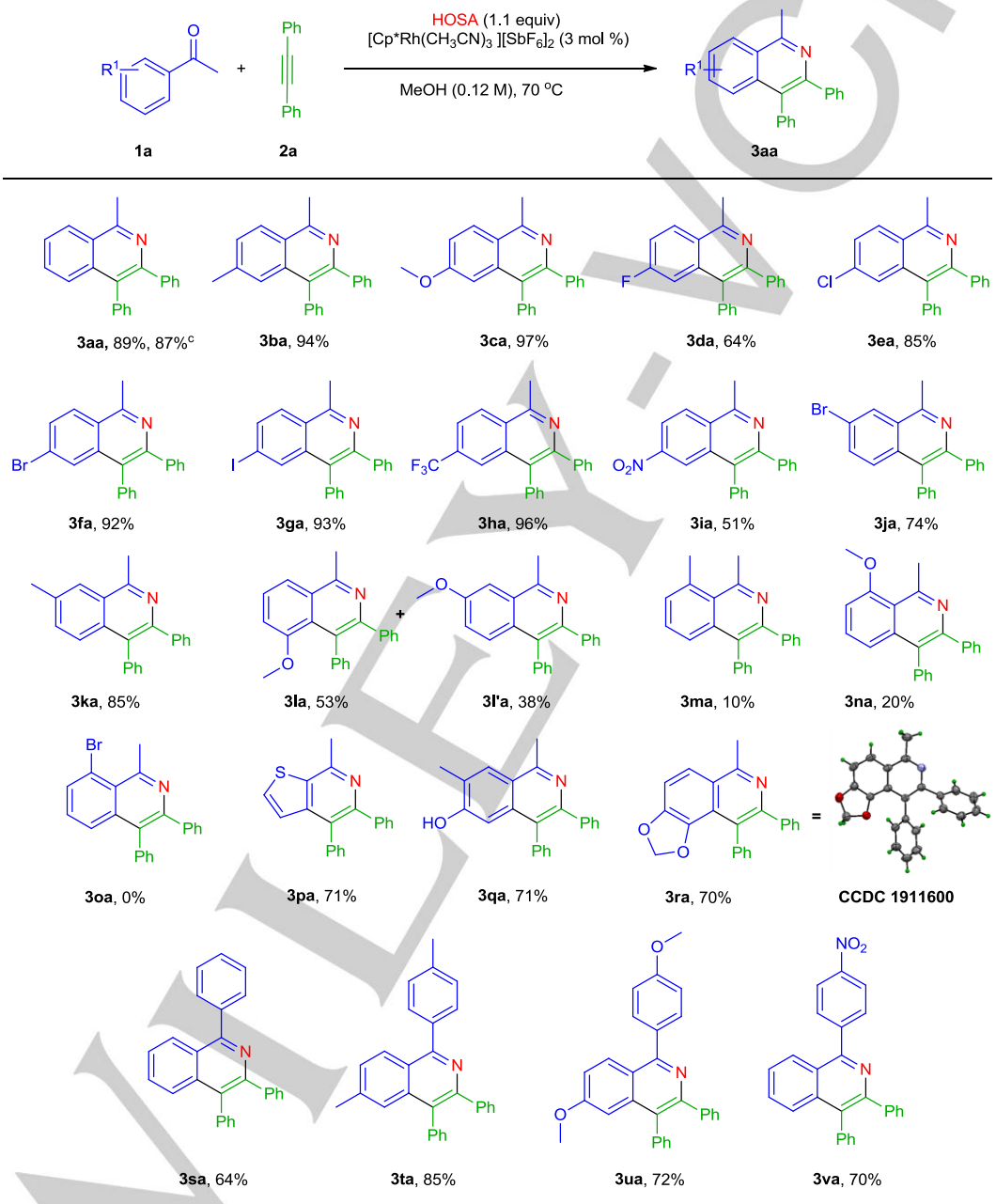
Scheme 2. Comparison with reported redox-neutral directing groups. [a] [a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.13 mmol), directing group (0.11 mmol), Cp*Rh (3 mol %), MeOH (0.12 M), 70 °C, 10 h. nd = not detected.

Results and Discussion

To test our hypothesis, acetophenone and diphenylacetylene were taken as the model substrate and coupling partner respectively. To our delight, when acetophenone and diphenylacetylene were treated with HOSA (1.1 equiv) in the presence of 3 mol % of $[Cp^*RhCl_2]_2$ and 1 equivalent of KOAc, afforded the desired isoquinoline in 30% yield (Table 1, entry 1). Hexafluoroisopropanol and toluene were screened as solvents under the same conditions, but in neither case was any reaction observed (Table 1, entries 2-3). Then we changed various other weak bases such as NaOAc, LiOAc, CsOAc. The use of CsOAc improved the yield up to 61% (Table 1, entry 6). Various other catalysts such as $[Cp^*CoI_2]$, $Co(acac)_2$, $Co(acac)_3$, and $[RuCl_2(p\text{-cymene})]_2$ failed to produce the desired annulated product (Table 1, entries 7-10). We presumed that, the use of a reactive

cationic Rh-catalyst such as $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ might enhance the yield. Interestingly, this cationic Rh (III) catalyst afforded the product in 80% yield (Table 1, entry 11). To know the influence of extra additive in product yield, we performed a reaction in the absence any additive. Gratifyingly, a considerable improvement of yield was noticed under additive free condition (Table 1, entry 12). For further improvement of product yield, we screened the reaction at different temperatures ranging from 60 °C to 80 °C (Table 1, entries 13-15) and achieved excellent yield of 92% at 70 °C. We tested this one-pot protocol using other redox-neutral directing groups which showed inferior results as compared to HOSA (Scheme 2).

With this optimized conditions in hand, a variety of electronically different acetophenones were tested using diphenylacetylene as the coupling partner (Scheme 3). Except for *ortho*-substituted examples (**3ma**, **3na** and **3oa**), most acetophenones gave the isoquinolines in high yield. The poor yields were recorded with *ortho*-substituted acetophenones may



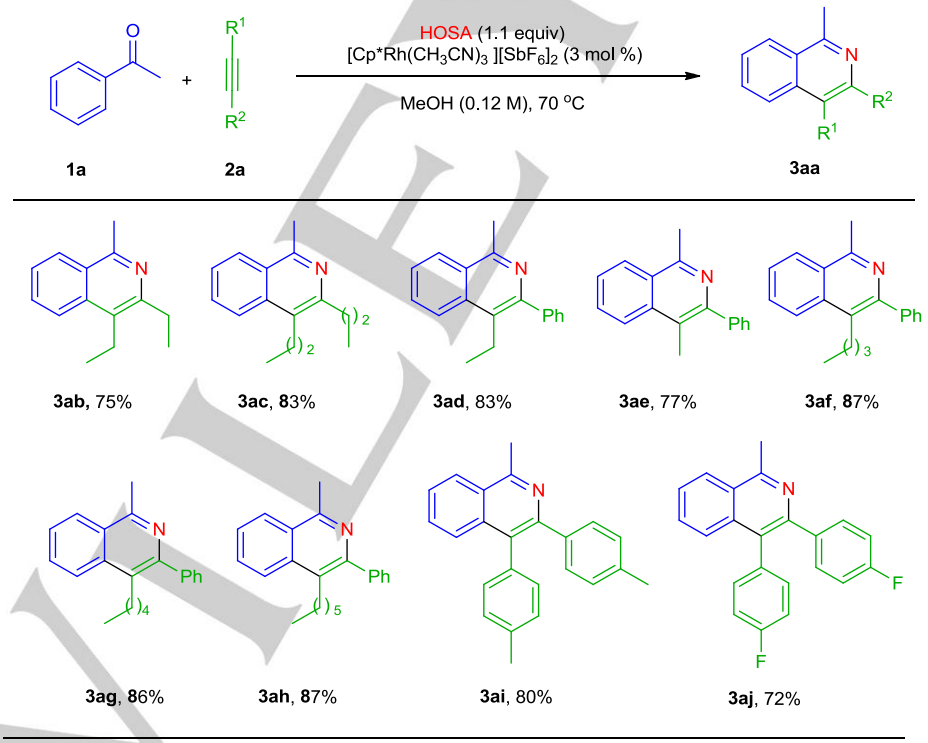
Scheme 3. Substrate and coupling parterner scope for one-pot synthesis of isoquinolines.[a], [b] [a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.13 mmol), HOSA (0.11 mmol), $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (3 mol %), MeOH (0.12 M), 70 °C, 10-20 h. [b] Isolated yields. [c] Isolated yield obtained from 1.00 mmol scale.

be due to steric hindrance near to the reaction site. Notably, **1r**, in which the alkoxy substituent is the part of a dioxolane ring produced the desired product **3ra** in 71% yield. The cyclic alkoxy group may be acting as a secondary directing group.[12] The

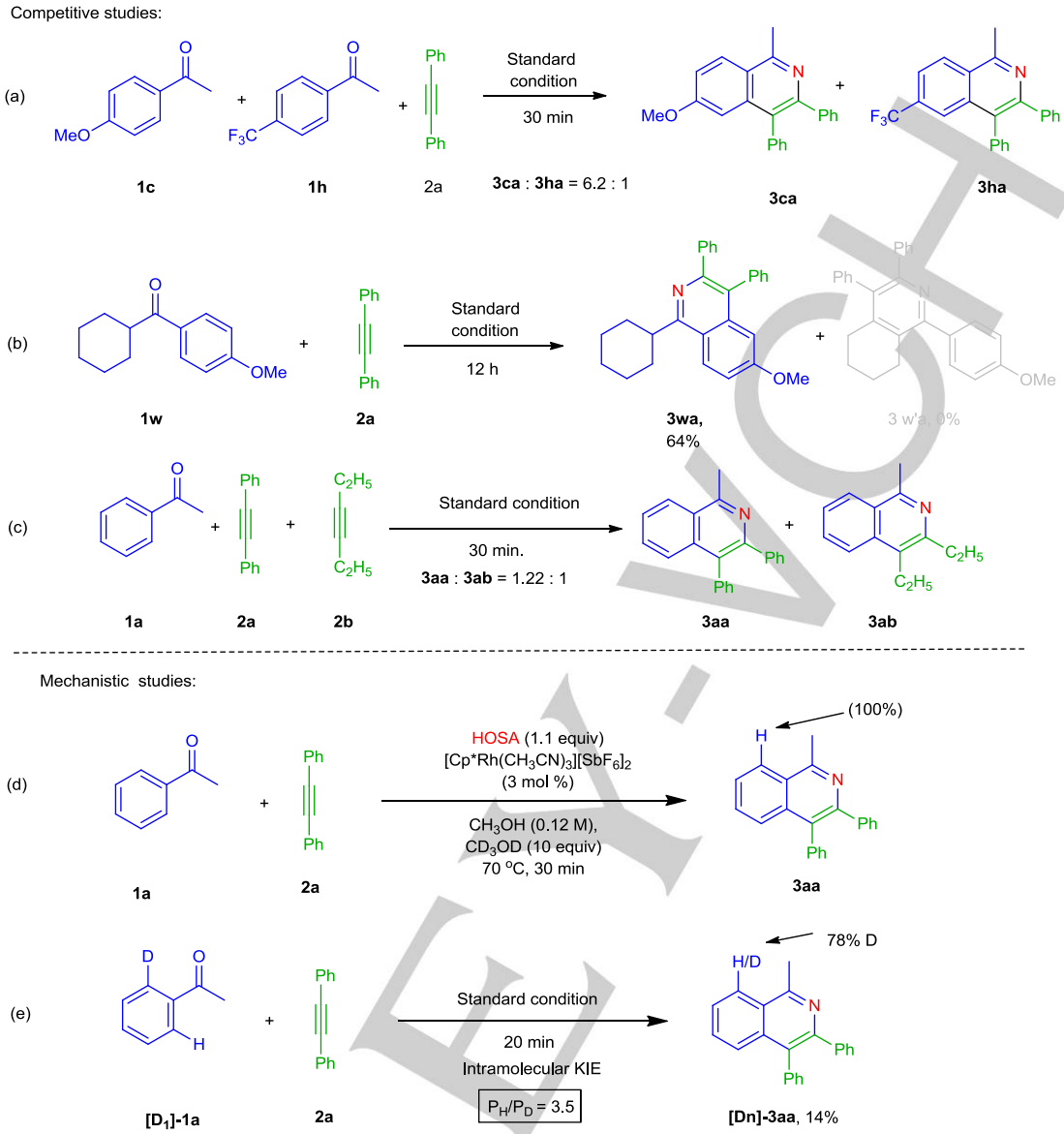
structure of **3ra** was confirmed by single crystal X-ray analysis.[13] With non-coordinating *meta*-substituents (*m*-Br and *m*-CH_3) the annulated products **3ja** and **3ka** were formed exclusively, positioning the *meta*-substituent as far as possible away from the alkyne substituents in the final product. Curiously, with an acetophenone containing the Lewis basic (*m*-OMe) group, a mixture of annulated products **3la** and **3l'a** were obtained in a 1.4:1 ratio, favouring the formation of isoquinoline with unfavourable peri interactions between the methoxy group of the acetophenone and a phenyl substituent of the alkyne. Although the product **3la** suffers from greater steric hindrance than **3l'a** in the intermediate pincer complex, the methoxy group may act as an additional donor ligand, stabilizing the Rh-complex and favouring the activation of the adjacent C-H bond. Halo-substituted acetophenones (**1d**, **1e**, **1f**, **1g** and **1j**) were also compatible with the reaction conditions, producing good to excellent yield of their respective annulated products (**3da**, **3ea**, **3fa**, **3ja** and **3ga**). Interestingly, the acetophenone **1q** bearing free hydroxyl group also worked efficiently giving **3qa** in 71% yield. Indeed, the optimized conditions worked well with heteroarylmethylketone **3p** giving **3pa** in good yield. Moreover, we also have performed the 1.00 mmol scale reaction applying the same general procedure with acetophenone **1a** which resulted 87% yield of **3aa**.

In addition, the scope of this methodology was evaluated with benzophenones (Scheme 3, **3sa**-**3va)**. Both symmetrical and unsymmetrical benzophenones afforded good yields of triarylisoquinolines. Especially, in the case of the 4-nitrophenylbenzophenone **3v**, annulation occurred only at the electron-rich phenyl ring of benzophenone, rather than the electron-deficient *para*-nitrophenyl, to give **3va** in 70% yield.

To extend the generality of this developed protocol, we further tested the reaction using different alkynes (Scheme 4, **3ab**-**3aj**). Dialkylalkynes (**3ab** and **3ac**), alkyl-aryl alkynes (**3ad**, **3ae**, **3af**, **3ag** and **3ah**) and diarylalkynes (**3ai** and **3aj**) all gave good yields. It is noteworthy that, in the case of alkyl-aryl alkynes, formation of a single regioisomer was observed where, the aryl ring is oriented towards the heteroatom of isoquinoline.[14] Formation of the selective regioisomeric product can be rationalized with the stabilization of the intermediate **III** (Scheme 6) by the phenyl ring through π-interaction with the metal orbitals. Notably, terminal alkynes (trimethylsilylacetylene, phenylacetylene) failed to produce the expected annulated products, possibly due to reaction with Cp*Rh(III) catalyst to produce dimeric alkynes.[15] Interestingly silylalkynes (bis(trimethylsilyl)acetylene, trimethylsilyl phenylacetylene) also failed. We presumed that, there may be protodesilylation pathway operating under the influence of acidic HOSA, which then produces terminal alkynes.



Scheme 4. Coupling parterner scope for one-pot synthesis of isoquinolines.[a], [b] [a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.13 mmol), HOSA (0.11 mmol), [Cp*Rh $(MeCN)_3$][SbF_6]$_2$ (3 mol %), MeOH (0.12 M), 70 °C, 10-20 h. [b] Isolated yields.



Scheme 5. Competitive and mechanistic studies.

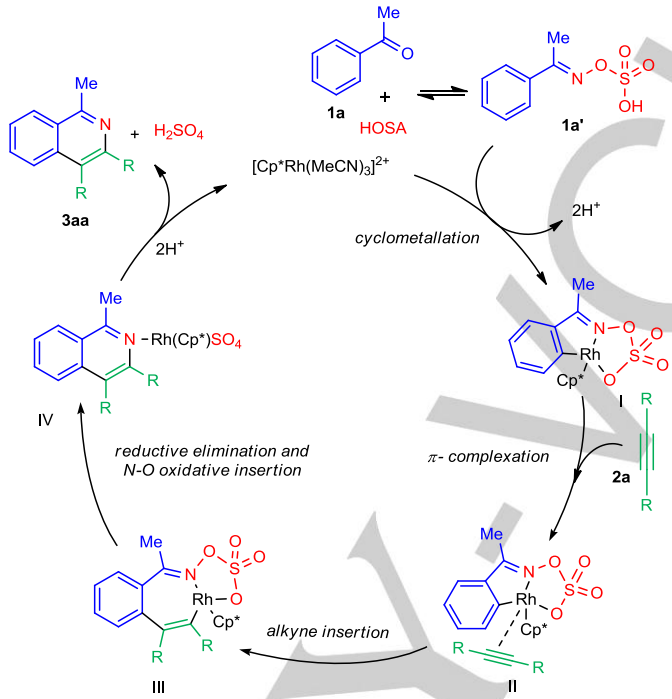
Competitive studies were carried out using a range of acetophenones and alkynes (Scheme 5, a-c) to elucidate how electronic effects influence the reactivity. First, an intermolecular competitive annulation reaction (Scheme 5, a) was performed between acetophenones **1c** (*para*-electron donating group), and **1h** (*para*-electron withdrawing group), which produced annulated products **3ca** and **3ha** in a ratio of 6.2:1. This experiment clearly indicated that cyclometallation-deprotonation is faster in electron-rich acetophenone **1c**.

Next, an intramolecular competitive Rh-insertion study was performed between sp^3-(cyclohexyl) and sp^2-(*para*-methoxyphenyl) C-H bonds, using ketone **1w**. Again, the experiment was conclusive, with **1w** undergoing exclusive sp^2 C-H activation to give **3wa** in 64% yield (Scheme 5, b). In an intermolecular competition between diphenylalkyne **2a** and diethylalkyne **2b**, comparable reactivity was observed between the two alkynes, that gave their respective annulated products **3aa** and **3ab** in 1.22:1.00 ratio (Scheme 5, c).

In order to better understand the catalytic activity of Cp^*Rh^{2+}, few kinetic experiments were conducted (Scheme 4, d-e). Initially, the standard condition was employed on **1a** with and without the use of the alkyne **2a** in 10 equiv of methanol-D_4, which showed no *ortho*-deuteriation on **3aa** and **1a** respectively (Scheme 5, d, details are in supporting information). These results reveal that the C-H activation step is irreversible. Moreover, we observed the Kinetic Isotope Effect (KIE) for the intra and intermolecular kinetic experiments to be 3.5 and 5.2 respectively (Scheme 5, e, and also see supporting information), suggesting that the initial C-H activation step may be the rate limiting step.[16]

Based on these experimental observations and literature precedents,[6h], [11c-d] we proposed a 5-stage catalytic cycle (Scheme 6). Initially, the cationic active catalyst, $[Cp^*Rh(MeCN)_3][SbF_6]_2$ undergoes cyclometallation with the in situ generated ketoxime **1a'** to form a five-membered rhodacycle

I, which after *π*-complexation with the alkyne **2a** gives intermediate **II**. Next, alkyne insertion occurs to afford the seven-membered rhodacycle **III**, which undergoes subsequent reductive elimination and N-O oxidative insertion to give **IV**. The last step of the catalytic cycle involves regeneration of active catalyst and formation of the desired annulated product **3aa** along with the by-product H_2SO_4. We presume that the acid generated in the final step reacts immediately with the product **3aa** and forms isoquinolinium salt. Proton NMR of the crude



Scheme 6. Proposed catalytic cycle.

mixture (filtering over celite pad) showed down field shift of methyl group signal in **3aa**, suggesting the formation of isoquinolinium salt in the crude mixture.

Conclusion

In summary, this is the first time HOSA has ever been used as a redox-neutral directing group for the synthesis of isoquinolines through C-H/N-O annulation from alkynes and the transient ketoxime. Moreover, it is simultaneously acting as an internal oxidant, in situ generated traceless directing group. Owing to these multiple advantages of this reagent, we believe that this reagent has much potential which can be use in various metal-catalyzed transformations.

Experimental Section

Acetophenone/benzophenone derivatives were bought from Sigma Aldrich, Alfa-Aesar, Avra, TCI and Spectrochem and used without any further purification. For column chromatography, silica gel (100–200 / 230-400 mesh) from Acme Co. was used. A gradient elution using distilled hexane and ethyl acetate was performed, based on Merck aluminium TLC sheets. All isolated compounds were characterized by ^{1}H NMR, ^{13}C NMR spectroscopy and HRMS. Copies of the ^{1}H NMR, ^{13}C NMR can be found in the Supporting Information. Nuclear Magnetic Resonance spectra were recorded on a Bruker 400 MHz and 700 MHz instrument.

All ^{1}H NMR experiments were reported in parts per million (ppm), and were measured relative to the signals for residual chloroform (7.26 ppm) in the deuterated solvent. All ^{13}C NMR spectra were reported in ppm relative to $CDCl_3$ (77.36 ppm).[17] Chemical shift multiplicities have represented as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), doublet of doublet (dd), doublet of triplet (dt), triplet of doublet (td). All crude NMR analysis were performed by using 1,3,5-trimthoxybenzene as the internal standard. X-ray crystallography was recorded at SCS, NISER, JATNI, BHUBANESWAR, India. $[D]_5$-acetophenone,[6f] $[D]_1$-acetophenone[6f] and $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$[18] were prepared by following the literature procedure.

Representative Procedure for the Annulation Reaction.

To an oven dried 25 mL schlenk tube, charged with a magnetic stirring bar, arylketone (0.1 mmol, 1 equiv), dry MeOH (0.12 M, 0.8 mL), hydroxylamine-*O*-Sulfonic acid (0.11 mmol, 1.1 equiv), $[Cp^*Rh(CH_3CN)_3][SbF_6]_2$ (0.003 mmol, 0.03 equiv) and alkyne (0.13 mmol, 1.3 equiv) were added under nitrogen atmosphere sequentially. The reaction mixture was allowed to stir (~500 rpm) at 70 °C in a pre-heated aluminium block. Reaction was monitored by TLC. After completion of the reaction (10-20 h), reaction mixture was transferred in to a 50 mL round bottom flask. The reaction vial was washed for two times with ethyl acetate/methanol. The solvent was removed under reduced pressure to get crude mixture and was extracted with ethyl acetate (3×10 mL) and saturated $NaHCO_3$. After brine wash, the organic layer was dried over anhydrous Na_2SO_4 and then purified through column chromatography by using 230-400 mesh silica, giving the product (**3aa**).

1-Methyl-3,4-diphenylisoquinoline (**3aa**).[6f] White solid (24 mg, 89% yield); R_f=0.4 (in 10% EtOAc/Hexane); m.p. 155-157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22-8.20 (m, 1H), 7.68-7.66 (m, 1H), 7.61-7.59 (m, 2H), 7.38-7.32 (m, 5H), 7.24-7.17 (m, 5H), 3.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.1, 149.8, 141.3, 137.9, 136.3, 131.7, 130.6, 130.2, 129.5, 128.5, 127.9, 127.5, 127.3, 126.9, 126.6, 126.5, 125.9, 23.0; HRMS (ESI) m/z: calcd for $C_{22}H_{18}N$ $[M+H]^+$ 296.1439; found, 296.1439.

1,6-Dimethyl-3,4-diphenylisoquinoline (**3ba**).[6f] White solid (29 mg, 94% yield); R_f=0.4 (in 10% EtOAc/Hexane); m.p.168-170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 9.2 Hz, 1H), 7.44-7.43 (m, 2H), 7.36-7.34 (m, 5H), 7.23-7.16 (m, 5H), 3.06 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7, 149.8, 141.4, 140.6, 138.0, 136.6, 131.8, 130.6, 129.1, 129.1, 128.5, 127.9, 127.4, 127.2, 125.8, 125.4, 124.9, 22.9, 22.5; HRMS (ESI) m/z: calcd for $C_{23}H_{20}N$ $[M+H]^+$ 310.1596; found, 310.1595.

6-Methoxy-1-methyl-3,4-diphenylisoquinoline (**3ca**).[6f] White solid (32 mg, 98% yield); m.p. 183-184 °C; R_f=0.6 (in 20% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.1 (d, *J* = 9.2 Hz, 1H), 7.36-7.3 (m, 5H), 7.23-7.17 (m, 6H), 6.91 (d, *J* = 2.8 Hz, 1H), 3.73 (s, 3H), 3.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 157.3, 150.4, 141.5, 138.3, 138.1, 131.6, 130.5, 128.6, 127.9, 127.7, 127.4, 127.2, 122.2, 119.0, 104.7, 55.5, 22.9; HRMS (ESI) m/z: calcd for $C_{23}H_{20}NO$ $[M+H]^+$ 326.1545; found, 326.1545.

6-Fluoro-1-methyl-3,4-diphenylisoquinoline (**3da**).[6f] White solid (20 mg, 64% yield); R_f=0.6 (in 10% EtOAc/Hexane); m.p. 140-142 °; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (dd, *J* = 9.2 Hz, 5.6 Hz, 1H), 7.39-7.32 (m, 6H), 7.29-7.26 (m, 1H), 7.23-7.20 (m, 5H), 3.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 162.3, 157.8, 150.7, 140.9, 138.4 (d, *J* = 9.6 Hz), 137.4, 131.5, 130.5, 129.3 (d, *J* = 5.2 Hz), 128.9 (d, *J* = 9.5 Hz), 128.7, 128.0, 127.7, 127.5, 123.7, 117.0 (d, *J* = 25.0 Hz), 110.2 (d, *J* = 22.1 Hz), 23.1; HRMS (ESI) m/z: calcd for $C_{22}H_{17}FN$ $[M+H]^+$ 314.1345; found, 314.1347.

6-Chloro-1-methyl-3,4-diphenylisoquinoline (**3ea**).[6f] White solid (28 mg, 85% yield); R_f=0.5 (in 10% EtOAc/Hexane); m.p. 179-181 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 9.2 Hz, 1H), 7.63 (d, *J* = 2.0 Hz, 1H), 7.53 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 7.38-7.34 (m, 5H), 7.22-7.17 (m, 5H), 3.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 150.9, 140.9, 137.5, 137.2, 136.7, 131.6, 130.5, 128.8, 128.7, 128.0, 127.8, 127.78, 127.7, 127.5, 125.5, 124.7, 23.0; HRMS (ESI) m/z: calcd for $C_{22}H_{17}ClN$ $[M+H]^+$ 330.1044; found, 314.1037.

6-Bromo-1-methyl-3,4-diphenylisoquinoline (**3fa**).[6f] White solid (36 mg, 96% yield);.m.p.183-185 °C. R_f=0.4 (in 10% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 4.8 Hz, 1H), 7.8 (s, 1H), 7.66 (dd, *J* = 5.2 Hz, 2.0 Hz, 1H), 7.37-7.34 (m, 5H), 7.21-7.18 (m, 5H), 3.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.1, 150.9, 140.9, 137.7, 137.1, 131.6, 130.5, 130.3, 128.74, 128.7, 128.6, 128.0, 127.8, 127.6, 127.5, 125.4, 124.9, 23.0; HRMS (ESI) m/z: calcd for $C_{22}H_{17}BrN$ $[M+H]^+$ 374.0544; found, 374.0552.

6-Iodo-1-methyl-3,4-diphenylisoquinoline (**3ga**). White solid (39 mg, 93% yield); R_f=0.5 (in 10% EtOAc/Hexane); m.p. 189-191 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.90 (d, *J* = 8.8 Hz, 1H), 7.85 (d, *J* = 8.8 Hz, 1H), 7.36-7.33 (m, 6H), 7.21-7.18 (m, 5H), 3.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 150.8, 140.9, 137.8, 137.1, 135.7, 135.4, 131.6, 130.5, 128.7, 128.3, 128.0, 127.8, 127.5, 127.3, 125.2, 98.0, 23.9. HRMS (ESI) m/z: calcd for $C_{22}H_{17}IN$ $[M+H]^+$ 422.0400; found, 422.0405.

6-(Trifluoromethyl)-1-methyl-3,4-diphenylisoquinoline (**3ha**).[6f] White solid (35 mg, 96% yield); R_f=0.6 (in 10% EtOAc/Hexane); m.p.114-116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, *J* = 8.8 Hz, 1H), 7.99 (s, 1H), 7.77 (dd, *J* = 8.4 Hz, 1.2 Hz, 1H), 7.39-7.37 (m, 5H), 7.24-7.21 (m, 5H), 3.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 151.2, 140.7, 136.8, 135.8, 132.0, 131.7, 131.6, 130.6, 130.1, 128.8, 128.1, 128.0, 127.7, 127.3, 127.2, 124.2 (q, *J* = 4.5 Hz), 122.8, 122.5 (q, *J* = 2.8 Hz), 23.1; HRMS (ESI) m/z: calcd for $C_{23}H_{17}F_3N$ $[M+H]^+$ 364.1308; found, 364.1305.

6-Nitro-1-methyl-3,4-diphenylisoquinoline (**3ia**).[6f] Yellow solid (17 mg, 51% yield); R_f=0.4 (in 10% EtOAc/Hexane); m.p. 173-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ δ 8.59 (s, 1H), 8.37-8.31 (m, 2H), 7.41-7.37 (m, 5H), 7.23-7.22 (m, 5H), 3.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 151.9, 148.6, 140.2, 136.3, 136.2, 131.5, 130.8, 130.5, 129.1, 128.4, 128.15, 128.1, 128.0, 123.1, 120.3, 23.2; HRMS (ESI) m/z: calcd for $C_{22}H_{17}N_2O_2$ $[M+H]^+$ is 341.1285; found, 341.1293.

7-Bromo-1-methyl-3,4-diphenylisoquinoline (**3ja**).[6f] White solid (28 mg, 74% yield); R_f=0.55 (in 10% EtOAc/Hexane); m.p. 132-135 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, *J* = 1.6 Hz, 1H), 7.55 (dd, *J* = 9.0 Hz, 1.7 Hz, 1H), 7.45 (d, *J* = 9.0 Hz, 1H), 7.28-7.25 (m, 5H), 7.12-7.09 (m, 5H), 3.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1, 150.2, 140.9, 137.3, 135.0, 133.6, 131.6, 130.5, 129.4, 128.7, 128.6, 128.2, 127.7, 127.6, 127.5, 120.8, 23.0; HRMS (ESI) m/z: calcd for $C_{22}H_{17}BrN$ $[M+H]^+$ 374.0544; found, 374.0545.

1,7-Dimethyl-3,4-diphenylisoquinoline (**3ka**).[6f] White solid (28 mg, 90% yield); R_f=0.4 (in 10% EtOAc/Hexane); m.p. 132-134 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.48 (d, *J* = 4.8 Hz, 1H), 7.35 (dd, *J* = 4.8 Hz, 0.5 Hz, 1H), 7.28-7.22 (m, 5H), 7.14-7.07 (m, 5H), 2.99 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 148.8, 141.1, 138.0, 136.9, 134.6, 132.6, 131.7, 130.6, 129.6, 128.5, 127.9, 127.4, 127.2, 126.7, 126.5, 124.9, 22.9, 22.2; HRMS (ESI) m/z: calcd for $C_{23}H_{20}N$ $[M+H]^+$ 310.1590; found, 310.1583.

5-Methoxy-1-methyl-3,4-diphenylisoquinoline (**3la**).[6a] White solid (17 mg, 53% yield); R_f=0.6 (in 20% EtOAc/Hexane); m.p. 151-153 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.8 (d, *J* = 8.4 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 6.8 Hz, 2H), 7.19-7.12 (m, 8H), 6.97 (d, *J* = 7.6 Hz, 1H), 3.4 (s, 3H), 3.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 157.2, 151.4, 141.9, 141.7, 130.7, 130.6, 128.2, 128.1, 127.8, 127.6, 127.4, 126.8, 125.9, 118.4, 110.4, 55.8, 23.7; HRMS (ESI) m/z: calcd for $C_{23}H_{20}NO$ $[M+H]^+$ 326.1545; found, 326.1518.

7-Methoxy-1-methyl-3,4-diphenylisoquinoline (**3l'a**).[6a] White solid (12 mg, 40% yield); R_f=0.5 (in 20% EtOAc/Hexane); m.p. 116-118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 9.2 Hz, 1H), 7.4 (d, *J* = 2.4 Hz, 1H), 7.37-7.33 (m, 5H), 7.24-7.15 (m, 6H), 3.99 (s, 3H), 3.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.2, 156.3, 148.1, 148.06, 141.3, 138.0, 131.7, 130.6, 129.5, 128.5, 128.4, 127.9, 127.7, 127.4, 127.1, 122.6, 103.8, 55.8, 23.2; HRMS (ESI) m/z: calcd for $C_{23}H_{20}NO$ $[M+H]^+$ 326.1545; found, 326.1548.

1,8-Dimethyl-3,4-diphenylisoquinoline (**3ma**). It was prepared according to the general procedure by taking the corresponding ketone in 0.2 mmol scale. White solid (6 mg, 10% yield); R_f=0.6 (in 10% EtOAc/Hexane); m.p. 121-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.2 Hz, 1H), 7.38-7.30 (m, 7H), 7.20-7.10 (m, 5H), 3.24 (s, 3H), 3.0 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 148.9, 141.2, 138.6, 138.4, 136.3, 131.8, 130.52, 130.5, 129.8, 129.5, 128.5, 127.9, 127.5, 127.4, 127.3, 125.4, 30.0, 26.3; HRMS (ESI) m/z: calcd for $C_{23}H_{20}N$ $[M+H]^+$ 310.1590; found, 310.1582.

8-Methoxy-1-methyl-3,4-diphenylisoquinoline (**3na**).[6a] White solid (7 mg, 20% yield); R_f=0.5 (in 10% EtOAc/Hexane); m.p. 149-151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 (t, *J* = 8.0 Hz, 1H), 7.37-7.3 (m, 5H), 7.22-7.16 (m, 6H), 6.90 (d, *J* = 7.6 Hz, 1H), 4.02 (s, 3H), 3.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 157.8, 149.8, 141.3, 139.2, 138.5, 131.8, 130.5, 130.4, 128.7, 128.5, 127.9, 127.3, 127.2, 119.4, 118.7, 106.7, 55.9, 29.6; HRMS (ESI) m/z: calcd for $C_{23}H_{20}NO$ $[M+H]^+$ is 326.1539; found, 326.1541.

7-Methyl-4,5-diphenylthieno[2,3-c]pyridine (**3pa**).[6e] White solid (21 mg, 71% yield); R_f=0.6 (in 10% EtOAc/Hexane); m.p. 153-155 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 5.4 Hz, 1H), 7.29-7.26 (m, 5H), 7.17-7.11 (m, 6H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 151.2, 146.1, 140.6, 138.5, 134.6, 131.4, 130.9, 130.7, 128.6, 128.6, 128.1, 127.5, 127.46, 124.6, 23.9; HRMS (ESI) m/z: calcd for $C_{20}H_{16}NS$ $[M+H]^+$ 302.0998; found, 302.0996.

1,7-Dimethyl-3,4-diphenylisoquinolin-6-ol (**3qa**). White solid (23 mg, 71% yield); R_f=0.70 (in 30% EtOAc/Hexane); m.p. 157-159 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ 9.1 (br, 1H), 7.90 (s, 1H), 7.29-7.25 (m, 4H), 7.23-7.18 (m, 3H), 7.1-7.16 (m, 3H), 6.90 (s, 1H), 2.96 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (175 MHz, $CDCl_3$ + DMSO- d_6): δ 158.3, 156.4, 149.0, 141.5, 138.8, 137.1, 131.7, 130.5, 128.7, 128.3, 128.0, 127.7, 127.3, 126.9, 121.7, 107.2, 22.6, 17.2; IR (neat): 3439, 3054, 2989, 2924, 2855, 2305, 1613, 1554, 1516, 1384, 1263, 1165, 898, 741,700 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{23}H_{20}NO$ $[M+H]^+$ 326.1539; found, 326.1534.

6-Methyl-8,9-diphenyl-[1,3]dioxolo[4,5-f]isoquinoline (**3ra**).[6f] White solid (25 mg, 74% yield); R_f=0.2 (in 10% EtOAc/Hexane); m.p. 248-249 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.7 Hz, 1H), 7.21-7.07 (m, 11H), 7.23 (s, 2H), 2.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.1, 150.2, 148.2, 142.1, 140.7, 138.6, 131.5, 130.6, 127.8, 127.4, 127.3, 127.2, 125.3, 123.5, 122.8, 121.4, 111.3, 101.8, 23.5; HRMS (ESI) m/z: calcd for $C_{23}H_{18}NO_2$ $[M+H]^+$ 340.1338; found, 340.1340. It was crystallized from dichloromethane.

1,3,4-Triphenylisoquinoline (**3sa**).[6g] White solid (23 mg, 64% yield); R_f=0.58 (in 10% EtOAc/Hexane); m.p. 181-183 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J* = 8.3 Hz, 1H), 7.82 (d, *J* = 6.8 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.61-7.49 (m, 5H), 7.43-7.29 (m, 7H), 7.19-7.15 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 150.0, 141.2, 140.1, 137.9, 137.3, 131.7, 130.8, 130.5, 130.3, 130.1, 128.9, 128.6, 127.9, 127.6, 127.3, 126.9, 126.3, 125.7; HRMS (ESI) m/z: calcd for $C_{27}H_{20}N$ $[M+H]^+$ 358.1596; found, 358.1598.

6-Methyl-3,4-diphenyl-1-(*p*-tolyl)isoquinoline (**3ta**).[19] White solid (33 mg, 85% yield); R_f=0.55 (in 20% DCM/Hexane); m.p. 171-173 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (dd, *J* = 8.4 Hz, 0.8 Hz, 1H), 7.75 (dd, *J* = 8.4 Hz, 1.2 Hz, 1H), 7.5 (s, 1H), 7.46-7.31 (m, 10H), 7.20-7.18 (m, 3H), 2.49 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.8, 150.1, 141.4, 140.5, 138.6, 138.1, 137.5, 137.4, 131.7, 130.8, 130.5, 129.4, 129.3, 129.0, 128.6, 127.8, 127.8, 127.5, 127.2, 125.1, 124.2, 22.4, 21.7. HRMS (ESI) m/z: calcd for $C_{29}H_{24}N$ $[M+H]^+$ 386.1909; found, 386.1918.

6-Methoxy-1-(4-methoxyphenyl)-3,4-diphenylisoquinoline (**3ua**).[6g] White solid (30 mg, 72% yield); R_f=0.43 (in 10% EtOAc/Hexane); m.p. 174-176 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 9.2 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.33-7.19 (m, 7H), 7.11-7.03 (m, 4H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 160.3, 159.1, 150.6, 141.5, 139.4, 138.3, 132.8, 131.8, 131.6, 130.7, 129.8, 129.0, 128.7, 127.8, 127.5, 127.2, 121.5, 119.1, 114.1, 104.5, 55.7, 55.5; HRMS (ESI) m/z: calcd for $C_{29}H_{24}NO_2$ $[M+H]^+$ is 418.1807; found, 418.1812.

1-(4-Nitrophenyl)-3,4-diphenylisoquinoline (**3va**). Pale yellow solid (32 mg, 80% yield); R_f=0.5 (in 60% DCM/Hexane); m.p. 179-181 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (d, *J* = 8.5 Hz, 2H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.57 (t, *J* = 15.0 Hz, 1H), 7.49 (t, *J* = 15.0 Hz, 1H), 7.34-7.31 (m, 5H), 7.23-7.21 (m, 2H), 7.13-7.11 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.5, 150.3, 148.3, 146.4, 140.7, 137.4, 137.4, 131.6, 131.5, 131.3, 130.7, 130.7, 128.8, 128.0, 127.9, 127.7, 127.6, 126.8, 126.8, 125.5, 123.9; HRMS (ESI) m/z calcd for $C_{27}H_{19}N_2O_2$ $[M+H]^+$ 403.1447; found, 403.1431.

1-Methyl-diethylisoquinoline (**3ab**). White solid (15 mg, 75% yield); R_f=0.4 (in 10% EtOAc/Hexane); m.p. 57-59 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 4 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 1H), 7.66 (t, *J* = 7.2 Hz, 1H), 7.5 (t, *J* = 7.2 Hz, 1H), 3.05 (q, *J* = 7.2 Hz, 2H), 2.97 (q, *J* = 7.2 Hz, 2H), 2.92 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1, 152.8, 135.5, 129.9, 127.6, 126.5, 126.4, 125.6, 123.7, 28.8, 22.6, 21.0, 15.6, 15.3. HRMS (ESI) m/z: calcd for $C_{14}H_{18}N$ $[M+H]^+$ 200.1439; found, 200.1440.

1-Methyl-dipropylisoquinoline (**3ac**).[6e] Colourless liquid (19 mg, 83% yield); R_f=0.6 (in 10% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.4 Hz, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 7.65 (td, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.5 (td, *J* = 8.0 Hz, 0.8 Hz, 1H), 2.98 (t, *J* = 7.6 Hz, 2H), 2.93-2.89 (m, 5H), 1.80 (sext, *J* = 8 Hz, 2H), 1.67 (sext, *J* = 8.0 Hz, 2H), 1.09 (t, *J* = 7.2 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9, 151.9, 135.8, 129.8, 126.6, 126.4, 126.3, 125.6, 123.9, 37.7, 30.1, 24.5, 24.2, 22.6, 14.9, 14.7; HRMS (ESI) m/z: calcd for $C_{16}H_{22}N$ $[M+H]^+$ 228.1747; found, 228.1745.

1-Methyl-3-ethyl-4-phenylisoquinoline (**3ad**).[6e] White solid (21 mg, 83% yield); R_f= 0.5 (in 10% EtOAc/Hexane); m.p; 122-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J* = 7.6 Hz, 1H), 8.90 (d, *J* = 8.8 Hz, 1H), 7.75 (t, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.52 (d, *J* = 7.2 Hz, 2H), 7.47 (t, *J* = 7.2 Hz, 2H), 7.4 (t, *J* = 7.2 Hz, 1H), 3.03-2.98 (m, 5H), 1.27 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 153.0, 138.2, 136.5, 130.7, 130.0, 129.1, 128.8, 127.7, 126.2, 126.1, 125.8, 125.7, 29.3, 22.8, 15.3; HRMS (ESI) m/z: calcd for $C_{18}H_{18}N$ $[M+H]^+$ 248.1424; found, 248.1427.

1,4-Dimethyl-3-phenylisoquinoline (**3ae**).[6f] Pale yellow solid (29 mg, 75% yield); R_f=0.48 (in 10% EtOAc/Hexane); m.p. 100-103 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 8.8 Hz, 1H), 7.75 (t, *J* = 7.6 Hz, 1H), 7.61-7.58 (m, 3H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 1H), 3.00 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 151.0, 142.0, 136.6, 130.2, 128.4, 127.7, 126.6, 126.5, 126.4, 124.4, 122.5, 22.8, 15.7; HRMS (ESI) m/z: calcd for $C_{17}H_{18}N$ $[M+H]^+$ 234.1277; found, 234.1289.

4-Butyl-1-methyl-3-phenylisoquinoline (**3af**). Oily liquid (28 mg, 83% yield); R_f=0.35 (in 10% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.74 (t, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 3H), 7.52-7.44 (m, 4H), 7.40 (t, *J* = 7.2 Hz, 1H), 2.98-2.95 (m, 5H), 1.65-1.59 (m, 2H), 1.36-1.31 (m, 2H), 0.85 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1, 151.2, 142.1, 135.7, 130.1, 129.7, 128.4, 127.8, 127.7, 127.0, 126.6, 126.5, 124.6, 33.7, 28.6, 23.3, 22.8, 14.1; IR (neat): 3424, 3067, 3026, 2956, 2926, 2869, 2359, 1723, 1614, 1563, 1503, 1463, 1439, 1391, 1333, 1274, 1155, 1101, 1072, 1029, 853, 792, 758, 701, 616 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{20}H_{22}N$ $[M+H]^+$ 276.1747; found, 276.1743.

1-Methyl-4-pentyl-3-phenylisoquinoline (**3ag**). Oily liquid (29 mg, 85% yield); R_f=0.4 (in 10% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.74 (t, *J* = 8.4 Hz, 1H), 7.59 (t, *J* = 8 Hz, 3H), 7.52-7.45 (m, 4H), 7.39 (t, *J* = 7.2 Hz, 1H), 2.98-2.94 (m, 5H), 1.69-1.61 (m, 2H), 1.34-1.21 (m, 4H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1, 151.2, 142.2, 135.7, 130.1, 129.6, 128.4, 127.8, 127.7, 127.0, 126.6, 126.5, 124.5, 32.4, 31.2, 28.8, 22.8, 22.6, 14.3; IR (neat): 3424, 3067, 2955, 2926,2868, 1726, 1614, 1563, 1503, 1440, 1391, 1333, 1266, 1122, 1072, 1050, 1029, 982, 962, 869, 805, 789, 758, 736, 701, 618, 592 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{21}H_{24}N$ $[M+H]^+$ 290.1903; found, 290.1899.

4-Hexyl-1-methyl-3-phenylisoquinoline (**3ah**). Oily liquid (26 mg, 87% yield); R_f=0.4 (in 10% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.51-7.36 (m, 5H), 2.97-2.93 (m, 5H), 1.67-1.59 (m, 2H), 1.34-1.18 (m, 6H), 0.86-0.82 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.7, 150.9, 141.8, 135.3, 129.7, 129.3, 128.1, 127.4, 127.3, 126.6, 126.2, 126.1, 124.2, 31.3, 31.2, 29.5, 28.5, 22.5, 22.4, 14.0; HRMS (ESI) m/z: calcd for $C_{22}H_{26}N$ $[M+H]^+$ 304.2050; found, 304.2060.

1-Methyl-3,4-di-p-tolylisoquinoline (**3ai**).[6f] Pale yellow solid (31 mg, 80% yield); R_f=0.5 (in 10% EtOAc/Hexane); m.p. 151-154 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19-8.17 (m, 1H), 7.68-7.66 (m, 1H), 7.78-7.55 (m, 2H), 7.3 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 7.6 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 7.6 Hz, 2H), 3.07 (s, 3H), 2.40 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.7, 149.7, 138.6, 136.9, 136.8, 136.6, 135.0, 131.5, 130.5, 130.0, 129.3, 129.2, 128.7, 126.6, 126.4, 125.8, 23.0, 21.6, 21.5; HRMS (ESI) m/z: calcd for $C_{24}H_{22}N$ $[M+H]^+$ 324.1747; found, 324.1761.

3,4-Bis(4-fluorophenyl)-1-methylisoquinoline (**3aj**).[6f] Pale yellow solid (28 mg, 72% yield); m.p. 143-145 °C; R_f=0.55 (in 10% EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22-8.20 (m, 1H), 7.62-7.61 (m, 3H), 7.35-7.31 (m, 2H), 7.20-7.17 (m, 2H), 7.10 (t, *J* = 8.8 Hz, 2H), 6.91 (t, *J* = 8.8 Hz, 2H), 3.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6 (d, *J* = 8.0 Hz), 161.1 (d, *J* = 7.7 Hz), 158.4, 148.9, 137.2 (d, *J* = 3.3 Hz), 137.3, 133.6 (d, *J* = 3.5 Hz), 133.2 (d, *J* = 7.9 Hz), 132.3 (d, *J* = 8.1 Hz), 130.5, 128.4, 127.1, 126.5, 126.2, 126.0, 115.8 (d, *J* = 21.0 Hz), 115.0 (d, *J* = 21.0 Hz), 23.0; HRMS (ESI) m/z: calcd for $C_{22}H_{16}F_2N$ $[M+H]^+$ 332,1245; found, 333.1244.

1-Cyclohexyl-6-methoxy-3,4-diphenylisoquinoline (**3wa**). Colurless oily liquid (32 mg, 64% yield); R_f=0.45 (in 5% EtOAc/Hexane); ^{1}H NMR (700 MHz, $CDCl_3$): δ 8.20 (d, *J* = 9.1 Hz, 1H), 7.42 (d, *J* = 6.3 Hz, 2H), 7.36 (t, *J* = 7.0 Hz, 2H), 7.33 (t, *J* = 7.0 Hz, 1H), 7.23 (d, *J* = 7.0 Hz, 2H), 7.20-7.16 (m, 4H), 6.93 (d, *J* = 2.1 Hz, 1H), 3.7 (s, 3H), 3.58-3.55 (m, 1H), 2.05 (d, *J* = 12.6 Hz, 2H), 2.00-1.94 (m, 4H), 1.82 (d, *J* = 12.6 Hz, 1H), 1.56 (q, *J* = 13.3 Hz, 3H); ^{13}C NMR (175 MHz, $CDCl_3$): δ 164.2, 160.4, 149.7, 141.8, 138.9, 138.7, 131.7, 130.9, 128.7, 128.0, 127.7, 127.4, 127.1, 126.8, 120.9, 118.7, 105.1, 55.5, 42.2, 32.8, 27.3, 26.6; IR (neat): 3427, 2925, 2852, 1617, 1574, 1502, 1410, 1373, 1264, 1235, 1030, 738, 700 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{28}H_{28}NO$ $[M+H]^+$ 394.2171: found, 394.2153.

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Keywords: Hydroxylamine-*O*-sulfonic acid; Isoquinoline; Redox-neutral; Rhodium catalysis; C-H activation.

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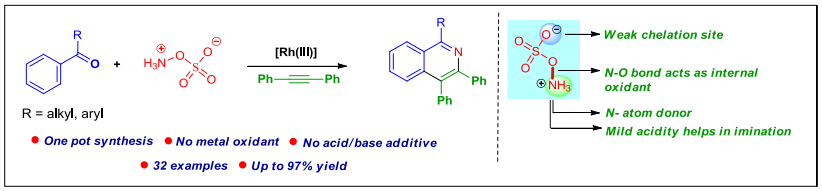
Entry for the Table of Contents

Key topic: C-H Activation



A new reactivity of hydroxylamine-*O*-sulfonic acid (HOSA) has been demonstrated as redox-neutral directing group for rhodium-catalyzed one-pot synthesis of diverse isoquinolines. This protocol reveals the utility of HOSA as a dircting group for the addditive free C-H/N-O annulations. Moreover the in situ cleavage of the directing group reduces one step making it as a step-economical process.