Organic LETTERS

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Cooperative Catalysis by Palladium–Nickel Binary Nanocluster for Suzuki–Miyaura Reaction of *Ortho*-Heterocycle-Tethered Sterically Hindered Aryl Bromides

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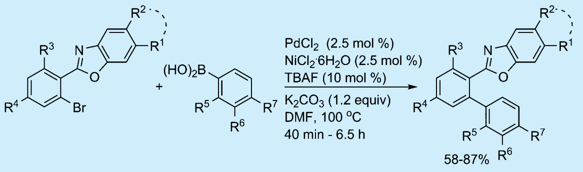
Ⓢ *Supporting Information*

ABSTRACT: The palladium–nickel binary nanocluster is reported as a new catalyst system for Suzuki–Miyaura cross-coupling of *ortho*-heterocycle-tethered sterically hindered aryl bromides. The inferior results obtained with the reported Pd/Ni salts/complexes or individual Pd/Ni nanoparticles as catalyst reveal the cooperative catalytic effect of the Pd and Ni nanoparticles in the Pd–Ni nanocluster. The broad substrate scope with respect to variation of the 2-arylbenzoxazole moiety and boronic acids, which offers a means for diversity generation and catalyst recyclability, marks a distinct advantage.



The 1,2-diaryl/arylheteroaryl-substituted heterocyclic framework has been recognized as the essential pharmacophoric feature of cyclooxygenase-2 (COX-2) selective inhibitors, typically known as coxibs, that have emerged as nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of rheumatoid arthritis.[1] However, the cardiovascular side effects associated with chronic administration of some of the coxibs led to their withdrawal from the market[2] and fueled a debate on the safe use of the existing COX-2 inhibitors[3] pressing the need for a novel anti-inflammatory scaffold. Toward this initiative, we recently reported 2-(2-arylphenyl)benzoxazoles as new anti-inflammatory chemotypes[4] affording new leads (Figure 1).

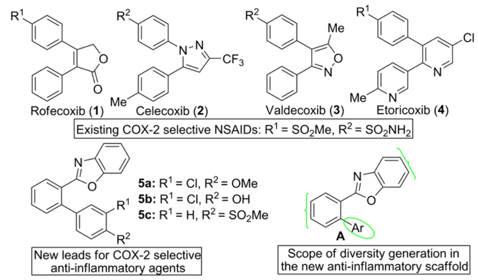
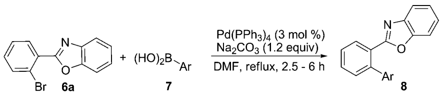


Figure 1. Representative COX-2 inhibitors and new leads.

The new anti-inflammatory leads (**5a**–**c**) were synthesized following the Suzuki–Miyaura cross-coupling (Scheme 1). For lead optimization it is necessary to generate diversity with the newly identified scaffold **A** (Figure 1) through modification on the (i) central aromatic ring incorporating substitution, (ii) benzoxazole moiety, introducing substitution in the phenyl ring as well as replacing it with naphthoxazole, and (iii) the 2-aryl group by replacing it with heteroaryl moiety. In view of the longer reaction time required in the reported procedure,[4] it becomes necessary to develop a more effective Suzuki–Miyaura cross-coupling protocol that would enrich the medicinal chemists' toolbox.[5]

Scheme 1. Suzuki–Miyaura Reaction of 6a with 7 To Form 8



It was observed that the Suzuki–Miyaura cross-coupling involving *ortho*-heterocycle-tethered sterically hindered substrates as the electrophilic coupling partner remained elusive.[6] Herein we report a binary palladium–nickel nanocluster (Pd–Ni NC) as a new and efficient catalyst system for Suzuki–Miyaura cross-coupling of *ortho*-heterocycle-tethered sterically hindered aryl bromides represented by the generalized structure **6**.

In search of a more effective catalytic system, the Suzuki cross-coupling of **6a**[7] with **7a** was performed separately in the presence of $Pd(OAc)_2$/(biphenyl)PCy_2 and $Pd(OAc)_2/PCy_3$ following the reported conditions[8] as well as under different variations by changing the solvent, but no significant improvement was observed (16–27 and 12–14% yields, respectively) (Supporting Information: entries 1–4, Table B).[9] Anticipating better catalytic potential of palladium nanoparticles (PdNPs),[10] the effect of the PdNPs was assessed using various Pd compounds (2.5 mol %) such as $PdCl_2$, $Pd(OAc)_2$, $Pd(TFA)_2$, $Pd(acac)_2$, Na_2PdCl_4, and $PdCl_2(PPh_3)_2$ as the precatalysts[11] for the reaction of **6a** with **7a** but **8a** was obtained in poor (21–47%) yields (Supporting Information: entries 1–12 and 14–18, Table C).[9]

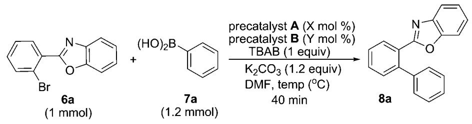
Received: February 24, 2014
Published: April 10, 2014

Being attracted by the recent trend toward nickel-catalyzed[12] Suzuki−Miyaura cross-coupling, various Ni compounds such as $NiCl_2·6H_2O$, $[NiCl_2(PPh_3)_2]$, and $NiSO_4$ were used (3 mol %) for the Suzuki cross-coupling of **6a** with **7a** in DMF at 130 °C or under reflux for 1 h that resulted **8a** in insignificant (0−18%) yields (Supporting Information: entries 1−6, Table D).[9] The use of $NiCl_2$−PCy_3 [so as to generate $NiCl_2(PCy_3)_2$ in situ] or $NiCl_2(PPh_3)_2$-PCy_3 under reported[13] as well as modified conditions with different solvents gave poor yields (19−28%) (Supporting Information: entries 5 and 6, Table B).[9] As NiNPs are also reported to catalyze the Suzuki−Miyaura coupling,[14] $NiCl_2·6H_2O$, $[NiCl_2(PPh_3)_2]$, and $NiSO_4$ were used as precatalysts for in situ formation of the NiNPs for the reaction of **6a** with **7a** but **8a** was obtained in poor yields (12−46%) (Supporting Information: entries 1−12, Table E).[9]

The ineffectiveness of the classical Suzuki−Miyaura cross-coupling reaction conditions using the Pd or Ni compounds and the lack of the desirable efficiency of the individual Pd and Ni NPs to promote the reaction of **6a** with **7a** to form **8a** in shorter reaction time led us to explore cooperative effects of the binary Pd−Ni NC. The high reactivity of isolated metal atoms makes them prone to form dinuclear species in contact with other metal centers involving their valence orbitals.[15] As Pd and Ni are elements of the same group with $4d^{10}5s^0$ and $3d^84s^2$ outer electronic configuration, respectively,[16] they are likely to get involved in Pd−Ni bonding during the nanocluster formation, with different electronic properties than that of the individual metal (Pd or Ni) NPs, and such a Pd−Ni binary NC may be a more effective catalyst.

Initial experiments on the use of 10 mol % each of $NiCl_2(PPh_3)_2$ and $PdCl_2(PPh_3)_2$ in the presence of K_2CO_3 (1.2 equiv) and TBAB (1 equiv) afforded **8a** in 74% yield in DMF at 130 °C for 40 min (Table 1, entry 1). The poor yields using $NiCl_2(PPh_3)_2$ or $PdCl_2(PPh_3)_2$ alone (entries 2 and 3, respectively) revealed the distinct cooperative catalytic effect of the Pd and Ni NPs in the binary Pd−Ni NC. The use of other Ni compounds such as $NiSO_4$ and $NiCl_2·6H_2O$ in place of $NiCl_2(PPh_3)_2$ but in combination with $PdCl_2(PPh_3)_2$ afforded **8a** in 26 and 62% yields, respectively (Table 1, entries 4 and 5). The replacement of $PdCl_2(PPh_3)_2$ by other Pd salts/complexes such as $[Pd(PPh_3)_4]$, $PdCl_2$, Na_2PdCl_4, $Pd(OAc)_2$, $Pd(TFA)_2$, $Pd(acac)_2$, $Pd(dba)_2$, and $Pd_2(dba)_3$ afforded **8a** in moderate (60−64%) yields (entries 6−12). The optimal amounts of the $NiCl_2(PPh_3)_2$ and $PdCl_2(PPh_3)_2$ could be reduced to 2.5 mol % each under the working temperature of 100 °C (entry 18). A decrease of the amount of $NiCl_2(PPh_3)_2$ and $PdCl_2(PPh_3)_2$ less than 2.5 mol % (entries 15−17) or the reaction temperature (entries 19−21) resulted in decreased yields. Further studies on optimization of various reaction parameters such as the use of various tetraalkylammonium salts as the stabilizer[17] (Supporting Information: Table H), different bases (Supporting Information: Table G), and solvents (Supporting Information: Table I) revealed that the best operative reaction condition is to use $NiCl_2·6H_2O$ (2.5 mol %) and $PdCl_2$ (2.5 mol %) in DMF in the presence of K_2CO_3 (1.2 equiv) and TBAF (10 mol %) at 100 °C for 40 min, which afforded **8a** in 80% yield (Supporting Information: entry 8, Table I).[9] The optimal Pd/Ni ratio was found to be 1:1, as a decrease in the product yield was observed in using higher amounts of Ni (Pd/Ni ratio increased to 1:2 and 1:4), while the increase of the Pd content (Pd/Ni ratio increased to 2:1 and 4:1) did not have any significant change in the product yield (Supporting Information: entries 48−51, Table F). The addition of external ligands such as PPh_3 or PCy_3 did not offer any improvement of the product yield (Supporting Information: footnotes c−h, Table F).[9]

Table 1. Suzuki Cross-Coupling of 6a with 7a To Form 8a in the Presence of Binary Pd−Ni NC Formed in Situ under Various Conditions[a]



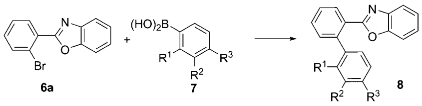
entry	precatalyst A (mol %)	precatalyst B (mol %)	temp (°C)	yield[b] (%)
1	$[NiCl_2(PPh_3)_2](10)$	$[PdCl_2(PPh_3)_2](10)$	130	74
2	$[NiCl_2(PPh_3)_2](10)$	none	130	27
3	none	$[PdCl_2(PPh_3)_2](10)$	130	30
4	$NiSO_4$ (10)	$[PdCl_2(PPh_3)_2](10)$	130	26
5	$NiCl_2·6H_2O$ (10)	$[PdCl_2(PPh_3)_2](10)$	130	62
6	$[NiCl_2(PPh_3)_2](10)$	$[Pd(PPh_3)_4](10)$	130	62
7	$[NiCl_2(PPh_3)_2](10)$	$PdCl_2(10)$	130	64
8	$[NiCl_2(PPh_3)_2](10)$	$Na_2PdCl_4(10)$	130	60
9	$[NiCl_2(PPh_3)_2](10)$	$Pd(OAc)_2(10)$	130	64
10	$[NiCl_2(PPh_3)_2](10)$	$Pd(TFA)_2(10)$	130	60
11	$[NiCl_2(PPh_3)_2](10)$	$Pd(acac)_2(10)$	130	61
12	$[NiCl_2(PPh_3)_2](10)$	Pd/C(10)	130	42
13	$[NiCl_2(PPh_3)_2](5)$	$[PdCl_2(PPh_3)_2](5)$	130	80
14	$[NiCl_2(PPh_3)_2](2.5)$	$[PdCl_2(PPh_3)_2](2.5)$	130	80
15	$[NiCl_2(PPh_3)_2](1)$	$[PdCl_2(PPh_3)_2](1)$	130	60
16	$[NiCl_2(PPh_3)_2](1)$	$[PdCl_2(PPh_3)_2](1)$	100	42
17	$[NiCl_2(PPh_3)_2](0.5)$	$[PdCl_2(PPh_3)_2](0.5)$	130	trace
18	$[NiCl_2(PPh_3)_2](2.5)$	$[PdCl_2(PPh_3)_2](2.5)$	100	76
19	$[NiCl_2(PPh_3)_2](2.5)$	$[PdCl_2(PPh_3)_2](2.5)$	80	63
20	$[NiCl_2(PPh_3)_2](2.5)$	$[PdCl_2(PPh_3)_2](2.5)$	60	32
21	$[NiCl_2(PPh_3)_2](2.5)$	$[PdCl_2(PPh_3)_2](2.5)$	40	trace
22	$[NiCl_2(PPh_3)_2](2.5)$	$[PdCl_2(PPh_3)_2](2.5)$	100	0[c]
23	$NiCl_2·6H_2O$ (2.5)	$[PdCl_2(PPh_3)_2](2.5)$	100	70
24	$NiCl_2·6H_2O$ 2.5)	$Pd(dba)_2(2.5)$	100	48
25	$NiCl_2·6H_2O$ (2.5)	$Pd_2(dba)_3(2.5)$	100	43
26	$[NiCl_2(PPh_3)_2](2.5)$	$PdCl_2(2.5)$	100	67
27	$NiCl_2·6H_2O$ (2.5)	$PdCl_2(2.5)$	100	74
28	$NiCl_2·6H_2O$ (2.5)	$PdCl_2(2.5)$	100	0[c]
29	none	none	100	0

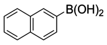
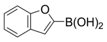
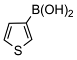
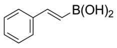
[a] **6a** (1.0 mmol) was treated with **7a** (1.2 mmol, 1.2 equiv) under the various conditions in DMF (2 mL) for 40 min. [b] Isolated yield of **8a**. [c] No K_2CO_3 was used.

The formation of the NPs was indicated by the color transition of the reaction medium from blue to dark brown to green to yellow in the initial stage of the reaction after the addition of all of the components. The formation of the Pd−Ni binary NC was confirmed by a high-resolution transmission electron microscopy (HRTEM) image of the reaction mixture after 10 min of mixing of all the components that showed the presence of 2.3−2.5 nm particles that have higher surface areas with highly accessible active sites and obviously will show enhanced properties due to the quantum size effects.[18] The identity of the particles was confirmed by energy dispersive acquired X-ray (EDAX).[9] The size of the Pd and Ni NPs formed separately/individually were on the order of 8−10 nm and 10−12 nm, respectively. Thus, the use of the mixed metal salts makes the reduction more feasible to form smaller MNPs. As Pd(II) has higher reduction potential (0.83 V) than that of Ni(II) (−0.23 V),[19] it acts as electron carrier and helps to reduce Ni(II).[20]

The cooperative catalytic effect of the Pd–Ni binary NC was extended to the Suzuki–Miyaura cross-coupling of **6a** with various substituted arylboronic acids (Table 2). The reaction condition was compatible with various functional groups, e.g., Cl, OCH_3, SCH_3, OCH_2Ph, CHO, NO_2, COMe, CO_2H, and CH_2OH. Sterically hindered 2-naphthylboronic acid underwent the cross-coupling efficiently. The successful reaction with the heteroaryl (entries 21 and 22), styryl (entry 23), and alkyl (entry 24) boronic acids demonstrate the broad substrate scope. In particular, the reaction of **6a** with 2-benzofuranboronic acid (entry 21) demonstrates the feasibility of the Pd–Ni NC to catalyze the Suzuki–Miyaura cross-coupling involving *ortho*-heterocycle-tethered sterically hindered aryl bromide with sterically hindered heteroaryl boronic acid. The use of $Pd(OAc)_2$ (1 mol %), PCy_3 (1.2 mol %), KF (3.3 equiv) in THF at rt for 4 h, akin to the reported catalyst system,[8b] failed to produce the Suzuki product for the reaction of **6a** with 2-benzofuranboronic acid, and only 19% yield was obtained in DMF at 100 °C for 4 h.[9]

Table 2. Suzuki–Miyaura Cross-Coupling of 6a with Various Arylboronic Acids Catalysed by Pd–Ni Binary NC[a]

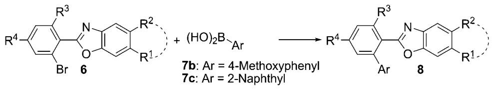


entry	boronic acid (**7**)	time (h)	yield (%)[b]
1	$R^1 = R^2 = R^3 = H$	0.66	80
2	$R^1 = R^2 = H, R^3 = OCH_3$	0.66	82
3	$R^1 = H, R^2 = R^3 = OCH_3$	0.66	81
4	$R^1 = R^2 = OCH_3, R^3 = H$	1.5	79
5	$R^1 = R^2 = H, R^3 = {}^tBu$	0.66	81
6	$R^1 = R^2 = H, R^3 = OCF_3$	1	75
7	$R^1 = R^2 = H, R^3 = SCH_3$	1.5	78
8	$R^1 = H, R^2 = Cl, R^3 = OCH_3$	1	81
9	$R^1 = H, R^2 = Cl, R^3 = O^iPr$	1	78
10	$R^1 = H, R^2 = Cl, R^3 = OBn$	1	84
11	$R^1 = R^2 = H, R^3 = CH_2OH$	1	87
12	$R^1 = R^2 = H, R^3 = F$	1.5	78
13	$R^1 = R^2 = H, R^3 = Cl$	1.5	76
14	$R^1 = R^2 = H, R^3 = CF_3$	1.5	77
15	$R^1 = R^2 = H, R^3 = CHO$	2.5	75
16	$R^1 = R^2 = H, R^3 = Ac$	2.5	70
17	$R^1 = R^2 = H, R^3 = CN$	2.5	78
18	$R^1 = R^2 = H, R^3 = CO_2H$	2.5	60
19	$R^1 = R^3 = H, R^2 = NO_2$	1.5	77
20		1	79
21		2	64
22		2	70
23		3.5	70
24	$MeB(OH)_2$	2	84

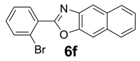
[a] **6a** (1.0 mmol) in DMF (2 mL) was treated with the various arylboronic acids (1.2 mmol, 1.2 equiv) in the presence of $NiCl_2·6H_2O$ (2.5 mol %), $PdCl_2$ (2.5 mol %), K_2CO_3 (1.2 equiv), and TBAF (10 mol %) at 100 °C. [b] Isolated yield of the corresponding biaryl **8**.

The scope of the reaction was further evaluated for different variation of the *ortho*-heterocycle-tethered aryl bromides **6** with 4-methoxyphenylboronic acid **7b** and 2-naphthylboronic acid **7c**, and the results (Table 3) demonstrated the broad substrate scope with respect to the variation of the heterocyclic scaffold as well as the aryl moiety bearing the electrophilic center.

Table 3. Pd–Ni NC-Catalyzed Suzuki–Miyaura Cross-Coupling of Different Variations of the *Ortho*-Heterocycle-Tethered Aryl Bromide 6 with 7b/7c[a]



7b: Ar = 4-Methoxyphenyl
7c: Ar = 2-Naphthyl

entry	bromide **6**	**7**	time (h)	yield (%)[b]
1	**6a**: $R^1 = R^2 = R^3 = R^4 = H$	**7b**	0.66	82
2	**6b**: $R^1 = CH_3, R^2 = R^3 = R^4 = H$	**7b**	0.66	75
3	**6c**: $R^1 = R^3 = R^4 = H, R^2 = CH_3$	**7b**	0.66	78
4	**6d**: $R^1 = R^2 = R^3 = H, R^4 = Cl$	**7b**	1	82
5	**6e**: $R^1 = R^2 = R^4 = H, R^3 = OH$	**7b**	6.5	58
6	 **6f**	**7b**	0.66	73
7		**7c**	4	67(19)[c]

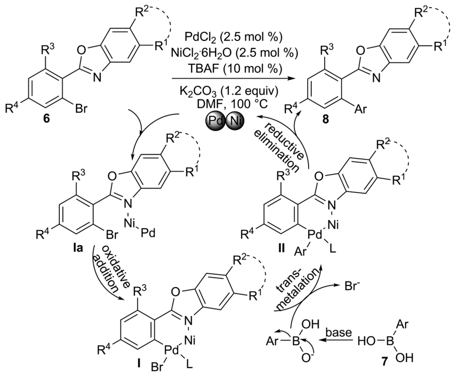
[a] **6** (1.0 mmol) in DMF (2 mL) was treated with **7b**/**7c** (1.2 mmol, 1.2 equiv) in the presence of $NiCl_2·6H_2O$ (2.5 mol %), $PdCl_2$ (2.5 mol %), K_2CO_3 (1.2 equiv), and TBAF (10 mol %) at 100 °C. [b] Isolated yield of the corresponding biaryl **8**. [c] The number in parentheses is the yield of the homocoupling product of the boronic acid.

The tolerability of the reaction conditions to the presence of Cl and OH groups signifies the chemoselectivity. The benzoxazole moiety can be replaced by a more sterically demanding naphthoxazole (entry 6, Table 3). The reaction of 2-(2-bromophenyl)naphthoxazole **6f** with **7c** (entry 7, Table 3) exemplify the reaction involving sterically hindered coupled partners. No significant amount of the Suzuki–Miyaura cross-coupling product was obtained during the reaction of **6f** with **7c** using $Pd(OAc)_2$ (1 mol %), PCy_3 (1.2 mol %), KF (3.3 equiv) in THF at rt for 4 h or in DMF at 100 °C for 4 h, akin to the reported catalyst system.[8b,9]

The Pd–Ni NC was recycled five times without a significant decrease in the catalytic activity. However, after the fifth cycle the recovered catalyst showed slightly lower activity (Supporting Information, Table O). The transmission electron microscopy (TEM) image of the catalyst system at this stage indicated the presence of slightly larger particles (4–6 nm).[9]

The possible role of the Pd–Ni NC's to catalyze the reaction is depicted in Scheme 2. Coordination with the N atom of the oxazole moiety of **6** with the hard Ni site (smaller in size than the larger and softer Pd atom) forms **Ia** and makes the Ni site electron rich. Transfer of the electron density from Ni to the larger and softer Pd site makes it more nucleophilic (electron rich), and thus, Pd oxidatively inserts into the C–Br bond to form the metallacycle **I**. The formation of the six-membered metallacycle with the Pd–Ni binary NC compared to the five-membered metallacycles in the case of either the PdNPs or the NiNPs also adds up to the cause of better catalytic potential of the binary NC apart from the cooperative effect of the Pd and Ni NPs in the binary Pd–Ni NC system. Subsequent ligand (Br^- anion) dissociation and base-induced transmetalation with the aryl moiety of the arylboronic acid **7** (through its anion) with **I** forms **II**. Reductive elimination from **II** gives rise to the product **8**

Scheme 2. Plausible Role of the Pd–Ni NC To Catalyze the Suzuki Cross-Coupling Reaction of 6 with 7 To Form 8



and regenerates the catalyst (Pd–Ni NC) to complete the catalytic cycle.

The lack of a significant amount of product formation in the absence of base (Table 1, entries 22 and 28) indicates its indispensable role in activating the arylboronic acid through proton abstraction[21] to increase the nucleophilicity of the corresponding aryl moiety and bind to the NP surface through the oxyanionic site to promote the transmetalation. However, K_2CO_3 could be replaced by CsF to make the Suzuki coupling effective, albeit in reduced yield (69%, Supporting Information, Table G)[9] as in aprotic polar medium the fluoride anion is capable of abstracting the proton[22] from the arylboronic acid.[23] Among the various solvents tried (Supporting Information, Table I),[9] the better yields (80 and 78%, respectively) in DMF and diethylformamide (DEF) could be due to their reducing ability to form the NPs.[24] This is reflected in the inferior results (50–70% yields)[9] obtained in other aprotic polar solvents such as DMA, DMSO, and NMP that are nonreducing, and as a result the base is competitively involved to form the Pd and Ni NPs.[25]

This work describes Pd–Ni binary NC as an efficient and recyclable catalyst system for Suzuki–Miyaura cross-coupling of *ortho*-heterocycle-tethered, sterically hindered aryl bromides. The inefficiency of the reported Pd/Ni catalysts and the individual Pd and Ni NPs signifies the ensembling effect of the Pd and Ni NPs in the Pd–Ni NC. The versatility is demonstrated using different variation of the (i) 2-aryl moiety of *ortho*-heterocycle-tethered aryl bromide, (ii) phenyl ring of the heterocycle scaffold, and (iii) boronic acid that mark the distinct advantages in diversity generation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Additional data, spectral data of all compounds, and scanned spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

K.S. thanks CSIR and DST (SR/S1/OC-33/2008), New Delhi, India, for a senior research fellowship.

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