catalysts

Communication

$H_3PW_{12}O_{40}$/SBA-15 for the Solventless Synthesis of 3-Substituted Indoles

Reza Tayebee [1,*], Adam F. Lee [2,*], Lucia Frattini [3] and Shahrebano Rostami [1]

[1] Department of Chemistry, School of Sciences, Hakim Sabzevari University, Sabzevar 96179-76487, Iran; rostami.shahrebano@gmail.com
[2] Applied Chemistry and Environmental Science, RMIT University, Melbourne VIC 3000, Australia;
[3] European Bioenergy Research Institute, Aston University, Aston Triangle B4 7ET, UK; lucia.frattini11@gmail.com
* Correspondence: rtayebee@hsu.ac.ir (R.T.); adam.lee2@rmit.edu.au (A.F.L.); Tel.: +98-51-44013212 (R.T. & A.F.L.)

Received: 27 March 2019; Accepted: 15 April 2019; Published: 30 April 2019

Abstract: A family of silica-supported $H_3PW_{12}O_{40}$ (HPW) solid acid catalysts was prepared by wet impregnation of mesoporous SBA-15 and investigated for the solventless synthesis of 3-substituted indoles under mild conditions. Mesoporous SBA-15 facilitated a high dispersion of immobilised $H_3PW_{12}O_{40}$, significantly improving the catalytic efficiency of the heteropolyacid for the desired multi-component transformation. The yield of 3-substituted indoles strongly correlated with HPW loading (which spanned 3.2–51.6 wt %) and corresponding acid strength; the 51.6 wt % HPW/SBA-15 delivered 81% yield of 2-[(1*H*-indol-3-yl)(phenyl)methyl]malononitrile, approximately five times greater than that of the unsupported HPW, and exhibited a broad substrate scope for aromatic aldehydes.

Keywords: $H_3PW_{12}O_{40}$; SBA-15; 3-substituted indole; condensation

1. Introduction

Porous solids find widespread application in heterogeneous catalysis as either active components or high-area support architectures, wherein pore dimensions and network connectivity control the attendant internal surface area and accessibility [1]. Microporous and mesoporous solid acids, such as zeolites, resins, and sulfonated carbons and silicas, facilitate dehydration, hydrolysis, condensation, and isomerization reactions pivotal to petroleum refining and fine and specialty chemical manufacturing [2]. However, the microporous nature and poor hydrothermal stability of the former render them unsuitable for transformation involving bulky substrates [3]. Among mesoporous silicas, the relatively large and tunable pore dimensions, thick walls, and high surface area of SBA-15 have rendered it an attractive support for sterically demanding organic transformations including biodiesel synthesis [4] and photodegradation of wastewater pollutants [5]. A range of catalytic functions have been incorporated into SBA-15 for acid-catalysed reactions including sulfated zirconia for ethyl levulinate production [6] and heteropolyacids for diesel desulfurization and fine chemicals production [7–9].

The 3-substituted indoles are important chemical intermediates in pharmaceuticals and contribute to the preparation of various pharmacochemical analogues of synthetic Ergine, Gramine and Sumatriptan [10,11]. Only a handful of catalyst systems, including Zn(salphen) [12], *N,N´*-dioxide Zn(II) [13], copper(II) sulfonato Salen [14] complexes and tetrabutylammonium fluoride [15], are reported for the synthesis of 3-substituted indoles. Herein, we demonstrate the application of $H_3PW_{12}O_{40}$-modified SBA-15 (HPW/SBA-15) as an effective solid acid catalyst for the solventless synthesis of 3-substituted indoles by the condensation of some aromatic aldehydes with indole and malononitrile under mild conditions. The high HPW dispersion achieved over the mesoporous silica offers a five-fold enhancement in the resulting yield of condensation products.

2. Results and Discussion

2.1. Physicochemical Properties of HPW/SBA-15

Successful immobilization of HPW over SBA-15 has been previously demonstrated by a range of bulk and surface characterization techniques, including N_2 porosimetry, elemental analysis, X-ray powder diffraction (XRD), X-ray photoelectron spectroscopy (XPS), high-resolution transmission electron microscopy (HRTEM) and ammonia and propylamine chemisorption [16]. The heteropolyacid content in the resulting family of HPW/SBA-15 materials can be readily varied between 4.3 and 51.6 wt % (3.2–38.2 wt % W, Table 1). Low loadings resulted in isolated Keggin clusters (Figure S1), which aggregated at loadings >9 wt % HPW to form crystalline secondary structures around 10 nm diameter. This coincided with a small decrease in the Brunauer Emmer-Teller (BET) surface area and a more significant fall in the pore volume (Figure S2) likely due to the blockage of micropores within the silica walls. HRTEM confirmed that Keggin units were uniformly dispersed throughout the ordered mesopore channels (Figure S3), and thermogravimetric analysis that these were thermally stable up to 380 °C [16], for all loadings. The resulting HPW/SBA-15 materials exhibited high acid densities.

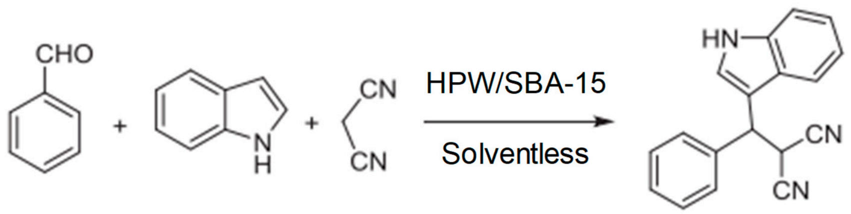
Table 1. $H_3PW_{12}O_{40}$ (HPW) content and crystallite size of HPW/SBA-15.

Catalyst	Bulk W Loading [a] (wt %)	Particle Size [b] (nm) [16]	Acid Loading [c] (mmol·g^{-1})
4.3 wt % HPW/SBA-15	3.2	10.5	0.21
12.1 wt % HPW/SBA-15	9.0	10.6	0.24
26.8 wt % HPW/SBA-15	19.9	10.7	0.29
51.6 wt % HPW/SBA-15	38.2	10.7	0.30

[a] XRF. [b] HRTEM. [c] NH_3 titration (unsupported $H_3PW_{12}O_{40}$ = 1 mmol·g^{-1}).

2.2. Catalytic Performance

HPW/SBA-15 samples displayed indole yields between 47 and 81%, which were strongly dependent on HPW loading. The synthesis of 2-[(1*H*-indol-3-yl)(phenyl)methyl]malononitrile from benzaldehyde, indole, and malononitrile (Scheme 1) was first monitored in the absence of any catalyst, resulting in only 9% of the desired product after 20 min (Table 2). In contrast, 44% yield was obtained in the presence of 5 mg pure HPW for the same reaction time and conditions. Immobilizing the heteropolyacid onto the surface of SBA-15 increased the dispersion of the catalytically active Brønsted acid sites throughout the silica pore network, resulting in increased specific (mass-normalised) activity. It is noteworthy that even the lowest loaded 4.3 wt % HPW/SBA-15 outperformed the pure HPW, presumably due to formation of large aggregates of HPW in the reaction mixture which led to a decrease in accessible acid sites, reflecting the importance of the so-called ‘pseudo-liquid phase’ catalysis for heteropolyacids in reactions involving low-polarity substrates. The substituted indole yield showed a strong correlation with the ammonia desorption temperature (Figure 1 and Figure S4), which in turn was directly proportional to the HPW loading and concomitant acid strength [16]; acidity increased with HPW loading due to the nucleation of isolated Keggin clusters (which lacked acid sites associated with water held within the secondary heteropolyacid structure) and the formation of two-dimensional HPW aggregates linked by crystalline water [17]. This structure–activity relation indicated that either the acid catalysed aldehyde activation or intramolecular cyclisation steps were rate-limiting for indole formation. In contrast, indole yield did not correlate with catalyst textural properties.



Scheme 1. General formulation for the preparation of 3-substituted indoles.

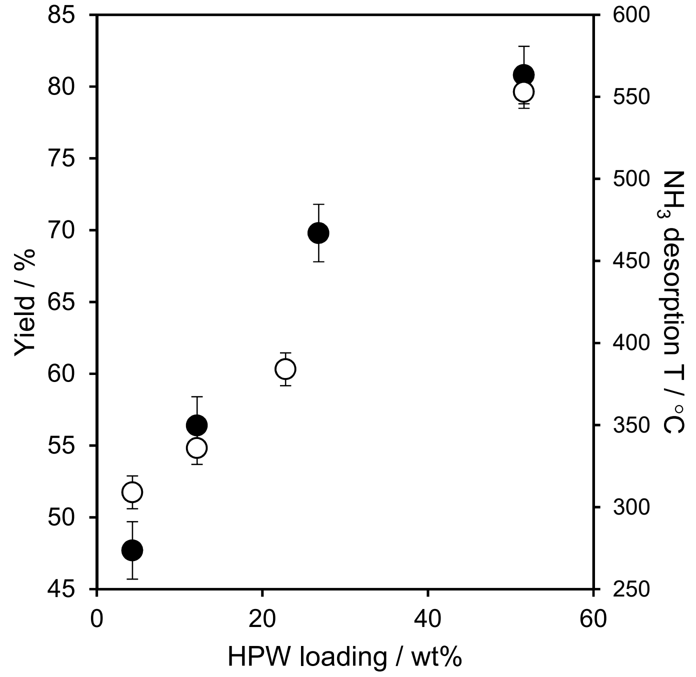


Figure 1. Dependence of 2-[(1*H*-indol-3-yl)(phenyl)methyl]malononitrile yield on HPW acid strength (determined from NH_3 TPD).

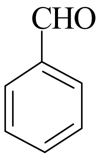
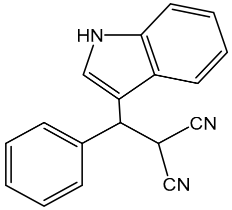
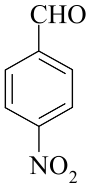
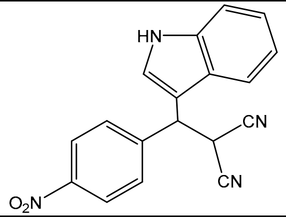
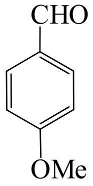
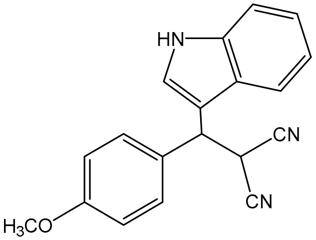
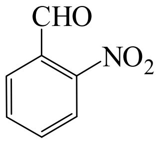
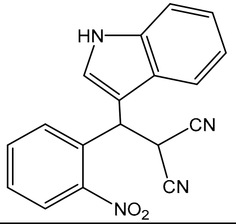
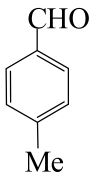
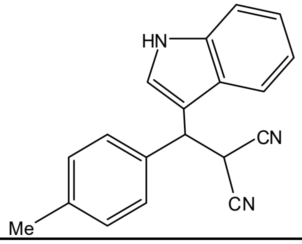
Table 2. Three-component solventless condensation of ethyl acetoacetate, urea and benzaldehyde catalysed by different catalysts.

Catalyst	Product Yield (%)
-	9
$H_3PW_{12}O_{40}$	44(17) [a]
4.3 wt % HPW/SBA-15	47
12.1 wt % HPW/SBA-15	56
25.2 wt % HPW/SBA-15	67
51.6 wt % HPW/SBA-15	81

Reaction conditions: aldehyde (1 mmol), malononitrile (1 mmol) and indole (1 mmol); 60 °C; 20 min; 5 mg catalyst. [a] 17 % yield was obtained with 2.59 mg of HPW.

The effectiveness of 51.6 wt % HPW/SBA-15 towards the synthesis of different 3-substituted indoles was evaluated for aromatic aldehydes possessing electron withdrawing and/or donating substituents. High yields for most of the aromatic aldehydes were obtained, as demonstrated in Table 3. However, electron-withdrawing groups afforded slightly better yields than electron-donating substituents [18,19].

Table 3. Three-component solventless condensation of ethyl acetoacetate, urea and aromatic aldehydes catalysed by 51.6 wt % HPW/SBA-15.

Entry	Aldehyde	Product	Yield (%)	m.p. (°C)
1			81	201–203
2			89	203–204
3			76	208–210
4			92	203–205
5			67	209–211

Reaction conditions as described in Table 2.

Hot-filtration tests evidenced negligible leaching of HPW from the surface of SBA-15. A reaction was performed with benzaldehyde at 60 °C for 10 min in the presence of 51.6 wt % HPW/SBA-15, at which point the product yield reached 52%. Ethanol (1 mL) was then added to the reaction mixture, and the heterogeneous catalyst was immediately removed by filtration. Thereafter, the remaining filtrate was monitored for additional 10 min at the same temperature, during which no significant increase in the product yield (<5%) was observed, confirming that there was no homogeneous contribution to the condensation reaction. The reproducibility and recyclability of 51.6 wt % HPW/SBA-15 for the preparation of 2-[(1*H*-indol-3-yl)(phenyl)methyl]malononitrile were also assessed. Triplicate reactions under identical conditions evidenced that product yields were reproducible within ±2% error. Catalyst reuse was undertaken by filtering the 51.6 wt % HPW/SBA-15 catalyst after the first run, washing with cold ethanol to remove residual organic species, drying at 90 °C for 4 h, and finally adding a fresh solution of the reactants. Good catalyst stability was observed, with only a ~15% decrease in product yield over five consecutive reactions (Figure S5).

Fourier transform infrared spectroscopy (FT-IR) of the post-reaction catalyst after five consecutive runs confirmed that the parent Keggin structure was preserved (Figure S6).

A plausible reaction pathway is proposed in Figure S7, in which a Knoevenagel condensation of the aldehyde carbonyl group with malononitrile forms intermediate (I) via nucleophilic addition. The indole then reacts with the olefinated intermediate (I) through a Michael addition to afford intermediate (II), which subsequently rearranges to the 3-substituted indole. The heteropolyacid likely protonates the carbonyl group of aromatic aldehydes, increasing its Lewis acidity. Electron-donating substituents on the phenyl ring of the aldehyde therefore deactivate it towards the nucleophilic attack of malononitrile, whereas electron-withdrawing groups activate the aldehyde [19,20].

3. Experimental

3.1. Catalyst Synthesis

$H_3PW_{12}O_{40}$ was dispersed over mesoporous SBA-15 (900 $m^2.g^{-1}$) via wet impregnation to achieve W loadings spanning 4.3–38.2 wt %, as described previously [16]. In brief, the required amount of HPW (Sigma-Aldrich, Gillingham, UK ≥99.9%) was dissolved in 30 mL methanol (Sigma-Aldrich, Gillingham, UK, HPLC grade) at room temperature. Thereafter, 1 g of the SBA-15 was added to the methanol solution and stirred overnight. The solvent was subsequently evaporated under vacuum at ambient temperature.

3.2. Catalyst Characterization and Synthesis of 2-[(1H-Indol-3-yl)(Aryl)methyl]Malononitriles

The catalysts used in this study were characterised in a previous publication [16]. Temperature programmed desorption (TPD) of ammonia-saturated samples was performed using a Quantachrome ChemBET3000 system (Quantachrome, Hook, UK) with a MKS Minilab MS detector (MKS, Crewe, UK). Samples (25–50 mg) were placed in a quartz U-shaped chemisorption cell and outgassed at 150 °C under flowing He (150 cm^3 min^{-1}) for 4 h prior to ammonia saturation with 10 vol % NH_3 in He at 100 °C. Ammonia desorption was subsequently performed under flowing He (150 $cm^3.min^{-1}$) between 100 and 800 °C, employing a ramp rate of 10 $°C.min^{-1}$.

For the preparation of 2-[(1*H*-indol-3-yl)(aryl)methyl]malononitriles, HPW/SBA-15 (5 mg) was thoroughly dispersed in a mixture of aldehyde (1.0 mmol), indole (1.0 mmol) and malononitrile (1.0 mmol), and the resulting heterogeneous mixture was heated to 60 °C. Indole (solid, m.p. 52–53 °C), aldehyde (liquid and/or solid), malononitrile (freshly crystallised) and the catalyst established a dense liquid ~0.3 mL. Progress of the reactions was screened by TLC (hexane/ethylacetate, 3:2). Finally, hot ethanol (3 mL) was added to the reaction mixture, and the heterogeneous catalyst was quickly filtered under stirring; then, the filtrate was cooled to 5 °C, and the precipitated product was gathered. Further purification of the desired products was achieved via re-crystallization in ethanol. Physical and spectroscopic properties of the pure products were compared with the corresponding known properties of 2-[(1*H*-indol-3-yl)(aryl)methyl]malononitriles [20,21].

4. Conclusions

A family of systematically related $H_3PW_{12}O_{40}$/SBA-15 catalysts, with HPW loadings ranging from 3.2 to 51.6 wt %, were prepared, characterised and applied for the solventless synthesis of 3-substituted indoles to understand the impact of support and acid strength on activity. Dispersing the HPW over a mesoporous silica support significantly promoted the desired multi-component transformation (yields of 47–81%) with respect to the unsupported parent HPW, which was attributed to improved active sites accessibility for isolated or low-dimensional Keggin nanostructures over SBA-15. The yield of 3-substituted indole was proportional to the acid strength, but poorly correlated with the textural properties. High HPW loadings, which offered the strongest acidity due to the stabilization of crystalline water within the secondary Keggin structure, exhibited good stability over five consecutive reactions and an almost five-fold improvement in the yield of 2-[(1*H*-indol-3-yl)(phenyl)methyl]malononitrile relative to unsupported HPW under mild conditions.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Figure S1: Powder XRD patterns for HPW/SBA-15 as a function of W loading, together with a pure HPW reference; Figure S2: Variation of (a) surface areas of HPW/SBA-15 and (b) mesopore diameter and mesopore volume of HPW/SBA-15 as a function of bulk W loading; Figure S3: HRTEM dark-field images of 3.2 wt % HPW/SBA-15 (a) and 51.6 wt % HPW/SBA-15 (b); Figure S4: NH_3 TPD spectra for HPW/SBA-15 as a function of W loading. Figure S5: Yield as a function of reusability for 51.6 wt % HPW/SBA-15; Figure S6: FT-IR spectra of 51.6 wt % HPW/SBA-15 after five consecutive reactions (a), fresh catalyst (b) post-reaction; Figure S7. Proposed reaction pathway for the condensation of aldehyde, indole and malononitrile; Table S1: Acid site densities of silica-supported HPW.

Author Contributions: R.T. and A.F.L. planned and designed the experiments. L.F. performed the catalyst synthesis and the characterization of catalysts. R.T. and S.R. performed the catalytic activity tests. R.T. wrote the manuscript. R.T. and A.F.L supervised the project and edited the manuscript. All authors discussed the results and approved the final version of the manuscript.

Funding: The work was supported by the Center for International Scientific Studies & Collaboration (CISSC), Aston and Hakim Sabzevari universities.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Taguchi, A.; Schüth, F. Ordered mesoporous materials in catalysis. *Micropor. Mesopor. Mater.* **2005**, *77*, 1–45.
2. Corma, A. Inorganic solid acids and their use in acid-catalyzed hydrocarbon reactions. *Chem. Rev.* **1995**, *95*, 559–614.
3. Rinaldi, R.; Schüth, F. Design of solid catalysts for the conversion of biomass. *Energy & Environmental Science* **2009**, *2*, 610–626.
4. Dacquin, J.-P.; Pirez, C.; Lee, A.F.; Wilson, K. Pore-expanded SBA-15 sulfonic acid silicas for biodiesel synthesis. *Chem. Comm.* **2012**, *48*, 212–214.
5. Tayebee, R.; Mohammadzadeh Kakhki, R.; Audebert, P.; Amini, M.M.; Salehi, M.; Mahdizadeh Ghohe, N.; Karimipour, G.R. A robust UV–visible light-driven SBA-15-PS/phthalhydrazide nanohybrid material with enhanced photocatalytic activity in the photodegradation of methyl orange. *Appl. Organomet. Chem.* **2018**, 32, e4391.
6. Morales, G.; Paniagua, M.; Iglesias, J.; Hernández, B.; Wilson, K.; Lee, A.F.; D.R. Brown, D.R.; Granollers, M.; Osatiashtiani, A.; Melero, J.A. Conformal sulfated zirconia monolayer catalysts for the one-pot synthesis of ethyl levulinate from glucose. *Chem. Comm.* **2014**, *50*, 11742–11745.
7. Tayebee, R.; Amini, M.M.; Pouyamanesh, S.; Aliakbari, A. A new inorganic–organic hybrid material Al-SBA-15-TPI/$H_6P_2W_{18}O_{62}$ catalyzed one-pot, three-component synthesis of 2*H*-indazolo [2,1-b] phthalazine-triones. *Dalton Trans.* **2015**, *44*, 5888–5897.
8. Julião, D.; Mirante, F.; Ribeiro, S.O.; Gomes, A.C.; Valença, R.; Ribeiro, J.C.; Balula, S.S. Deep oxidative desulfurization of diesel fuels using homogeneous and SBA-15-supported peroxophosphotungstate catalysts. *Fuel*, **2019**, *241*, 616–624.
9. Lucas, N.; Gurrala, L.; Athawale, A. Heteropolyacids supported on mesoporous AlSBA-15 as efficient catalysts for esterification of levulinic acid. *J. Por. Mater.*, *2019*, doi:10.1007/s10934-019-00734.
10. Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles: Structures, Reactions, Synthesis, and Applications*; Wiley-VCH: Weinheim, Germany, 2013; pp. 125–147.
11. Ziarani, G.M.; Moradi, R.; Ahmadi, T.; Lashgari, N. Recent advances in the application of indoles in multicomponent reactions. *RSC Adv.* **2018**, *8*, 12069–12103.
12. Anselmo, D.; Adán, E.C.E.; Belmonte, M.M.; Kleij, A.W. Zn-Mediated synthesis of 3-substituted indoles using a three-component reaction approach. *Eur. J. Inorg. Chem.*, **2012**, 4694.
13. Chen, W.; Cai, Y.; Fu, X.; Liu, X.; Lin, L.; Feng, X. Enantioselective one-pot synthesis of 2-amino-4-(indol-3-yl)-4H-chromenes. *Org. Lett.*, **2011**, *13*, 4910.
14. Qu, Y.; Ke, F.; Zhou, L.; Li, Z.; Xiang, H.; Wu, D.; Zhou, X. Synthesis of 3-indole derivatives by copper sulfonato Salen catalyzed three-component reactions in water. *Chem. Commun.*, **2011**, *47*, 3912.

15. Singh, N.; Allam, B.K.; Raghuvanshi, D.S.; Singh, K.N. An efficient tetrabutylammonium fluoride (TBAF)-catalyzed three-component synthesis of 3-substituted indole derivatives under solvent-free conditions. *Adv. Synth.Catal.*, **2013**, *355*, 1840.
16. Frattini, L.; Isaacs, M.A.; Parlett, C.M.; Wilson, K.; Kyriakou, G.; Lee, A.F. Support enhanced α-pinene isomerization over HPW/SBA-15. *Appl. Catal. B: Environ.* **2017**, *200*, 10–18.
17. Bardin, B.B.; Bordawekar, S.V.; Neurock, M.; Davis, R.J. Acidity of Keggin-Type Heteropolycompounds Evaluated by Catalytic Probe Reactions, Sorption Microcalorimetry, and Density Functional Quantum Chemical Calculations. *J. Phys. Chem. B* **1998**, 102, 10817–10825.
18. Wang, L.; Huang, M.; Zhu, X.; Wan, Y. Polyethylene glycol (PEG-200)-promoted sustainable one-pot three-component synthesis of 3-indole derivatives in water. *Appl. Catal. A: Gen.* **2013**, *454*, 160–163.
19. He, Y.-H.; Cao, J.-F.; Li, R.; Xiang, Y.; Yang, D.-C.; Guan, Z. L-Proline-catalyzed multicomponent synthesis of 3-indole derivatives. *Tetrahedron* **2015**, *71*, 9299–9306.
20. Rajesh, U.C.; Kholiya, R.; Thakur, A.; Rawat, D.S. [TBA][Gly] ionic liquid promoted multi-component synthesis of 3-substituted indoles and indolyl-4H-chromenes. *Tetrahedron Lett.* **2015**, *56*, 1790–1793.
21. Ghohe, N.M.; Tayebee, R.; Amini, M.M.; Osatiashtiani, A.; Isaacs, M.A.; Lee, A.F. $H_5PW_{10}V_2O_{40}$@VO_x/SBA-15-NH_2 catalyst for the solventless synthesis of 3-substituted indoles. *Tetrahedron* **2017**, *73*, 5862–5871.