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Ruthenium(II)-Catalyzed C−H Chalcogenation of Anilides

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Abstract. Ruthenium-catalyzed C−H chalcogenations of anilides with readily available diselenides and disulfides have been achieved. Our strategy features ample substrate scope, affording the mono-*ortho* selenylated and thiolated anilides with complete site selectivity control and high catalytic efficacy. Detailed mechanistic studies provide strong support for a facile base-assisted internal electrophilic substitution (BIES) metalation event.

Keywords: Selenylation; Thiolation; anilides; Ruthenium catalyst; C−H activation.

Introduction

Diaryl sulfide and diaryl selenide scaffolds are important structural motifs in a wide variety of functional molecules, drug candidates and medicinal chemistry because of their potential biological activities.[1] For example, various organoselenium and organosulfur compounds have been identified as important therapeutic compounds ranging from antiviral and anti-inflammatory to anticancer agents.[2] Furthermore, they also have significant applications to functional organic material,[3] fluorescent probes [4] and play an important role in organic synthesis.[4g] The preparation of aryl selenides therefore has attracted considerable interest in the past decades. Compared with a large number of synthetic methods of aryl selenides which are limited to the coupling of prefunctionalized aryl substrates [5] or electron-rich aryl compounds,[6] the transition-metal-catalyzed C−Se and C−S formation via direct C−H functionalization[7] represents a powerful and reliable procedure due to its remarkable potential for step economy and environmental sustainability.

Recently, numerous approaches to C−S or C−Se bond formation through chelation-assisted direct C−H thiolation and selenation catalyzed by palladium(II),[8] rhodium(III),[9] ruthenium,[10] nickel,[11] cobalt,[12] or copper[13] have been explored by Ackermann, Nishihara, Shi, Li, and Zhang. While these protocols provided efficient and convenient route to access various chalcogenated arenes, there are still some restrictions, such as long reaction time as well as harsh reaction conditions that may limit further applications. Especially, these previous methods are limited to pyrimidine, oxime or other N-containing directing groups, whereas the weakly-coordinating[14] O- or S-directing groups have rarely been reported (Scheme 1a).[15]

Anilides are useful building blocks in organic synthesis, medicinal chemistry, natural products and drug discovery. Importantly, acetanilide (antifebrin) and its derivatives are valuable antipyretic and analgesic drugs which are widely used in clinical practice.[16] Given the structural utility, highly efficient methods for transition metal-catalyzed C−H functionalization with anilides have been devised in recent years.[17]

Considering the versatile bioactivities of arylselenium and arylsulfur anilides, and in continuation of our recent silver-mediated C−H chalcogenations of pyrazones,[18] we herein report an efficient ruthenium-catalyzed C−H chalcogenations of anilides with easily available diselenides and disulfides under mild reaction conditions by weak coordination (Scheme 1b).

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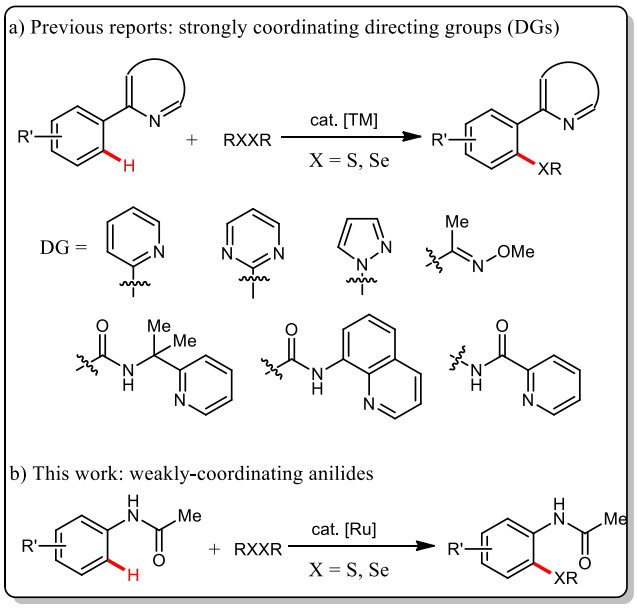


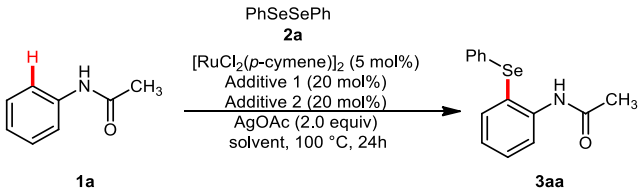
Scheme 1. Transition-metal-catalyzed C−H chalcogenation of arenes

Results and Discussion

Optimization studies

At the outset of our studies, we probed the effect exerted by various additives, and solvents on the oxidative C−H selenylation using *N*-phenylacetamide (**1a**) and 1,2-diphenyldiselane (**2a**) as the substrates at 100 ºC for 24 h. Preliminary studies indicated silver(I) acetate to be the most effective terminal oxidant (Table S-1 in the Supporting Information). Solvent optimization (Table 1, entries 1–9) showed that toluene was the ideal solvent, while other reaction media gave significantly lower yields. Among a variety of additives, $AgBF_4$ and $Cu(OTf)_2$ proved to be optimal (entries 10–17), respectively, which furnished the desired product **3aa** in 91% yield. Importantly, the triflate ion is crucial for this transformation.[17b] The yield decreased significantly without $AgBF_4$ additive, which indicated that the $AgBF_4$ might facilitate the formation of the active ruthenium catalyst species. Control experiments verified that in the absence of $[\{RuCl_2(p\text{-cymene})\}_2]$ or when $[\{RuCl_2(p\text{-cymene})\}_2]$ was replaced by palladium catalysts, the desired product **3aa** was obtained only in minor quantities (Table S-1 in the Supporting Information).

Table 1. Optimization of ruthenium-catalyzed C−H selenylation[a]



Entry	Additive **1**	Additive **2**	Solvent	Yield[b]
1	$AgSbF_6$	AgOTf	DCE	10
2	$AgSbF_6$	AgOTf	*t*AmOH	trace
3	$AgSbF_6$	AgOTf	dioxane	34
4	$AgSbF_6$	AgOTf	DMF	trace
5	$AgSbF_6$	AgOTf	DMSO	trace
6	$AgSbF_6$	AgOTf	CH_3CN	15
7	$AgSbF_6$	AgOTf	HFIP	trace
8	$AgSbF_6$	AgOTf	toluene	84
9	$AgSbF_6$	AgOTf	*o*-xylene	76
10	$AgSbF_6$	$Cu(OTf)_2$	toluene	85
11	$AgSbF_6$	CH_3SO_3H	toluene	trace
12	$AgSbF_6$	CF_3SO_3H	toluene	37
13	$AgBF_4$	AgOTf	toluene	89
14	KPF_6	AgOTf	toluene	55
15	HOAc	AgOTf	toluene	trace
16	CsOAc	AgOTf	toluene	trace
17	**$AgBF_4$**	**$Cu(OTf)_2$**	**toluene**	**91**
18	----	$Cu(OTf)_2$	toluene	63
19	$AgBF_4$	----	toluene	trace
20	$AgBF_4$	$Cu(OTf)_2$	toluene	77[c]
21	$AgBF_4$	$Cu(OTf)_2$	toluene	64[d]

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (2.0 equiv, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), solvent (2.0 ml), 24 h, under Ar. [b] Isolated yields. [c] 80 ºC. [d] 2.5 mol% $[\{RuCl_2(p\text{-cymene})\}_2]$.

Subsequently, we evaluated the effect of the *N*-substituent of the anilides **1** for the C–H selenylation (Scheme 2). Interestingly, the acetyl group appeared to be more effective as compared to more sterically hindered analogues **1b** or the aryl substituted anilide **1c** under the current reaction conditions. The more electron-withdrawing substituted amide **1d** did not provide the desired selenylated product. Further studies indicated that the tertiary amide **1e** failed to enable the reaction, highlighting the key importance of the acidic N–H moiety (Scheme 2).

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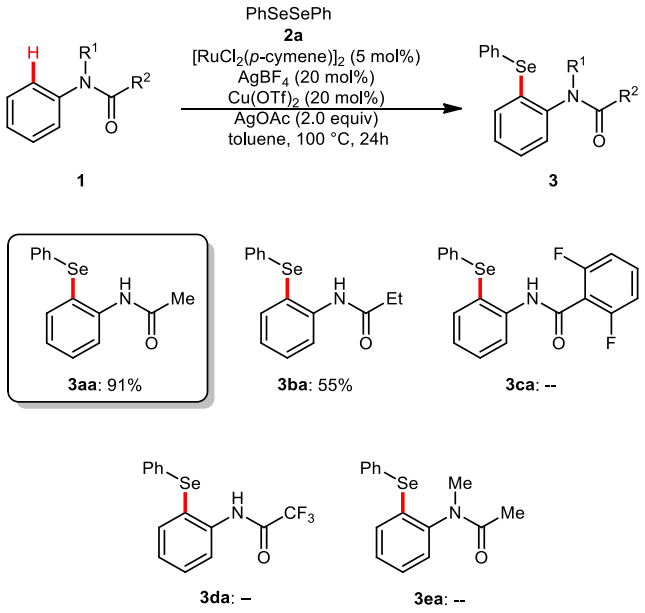
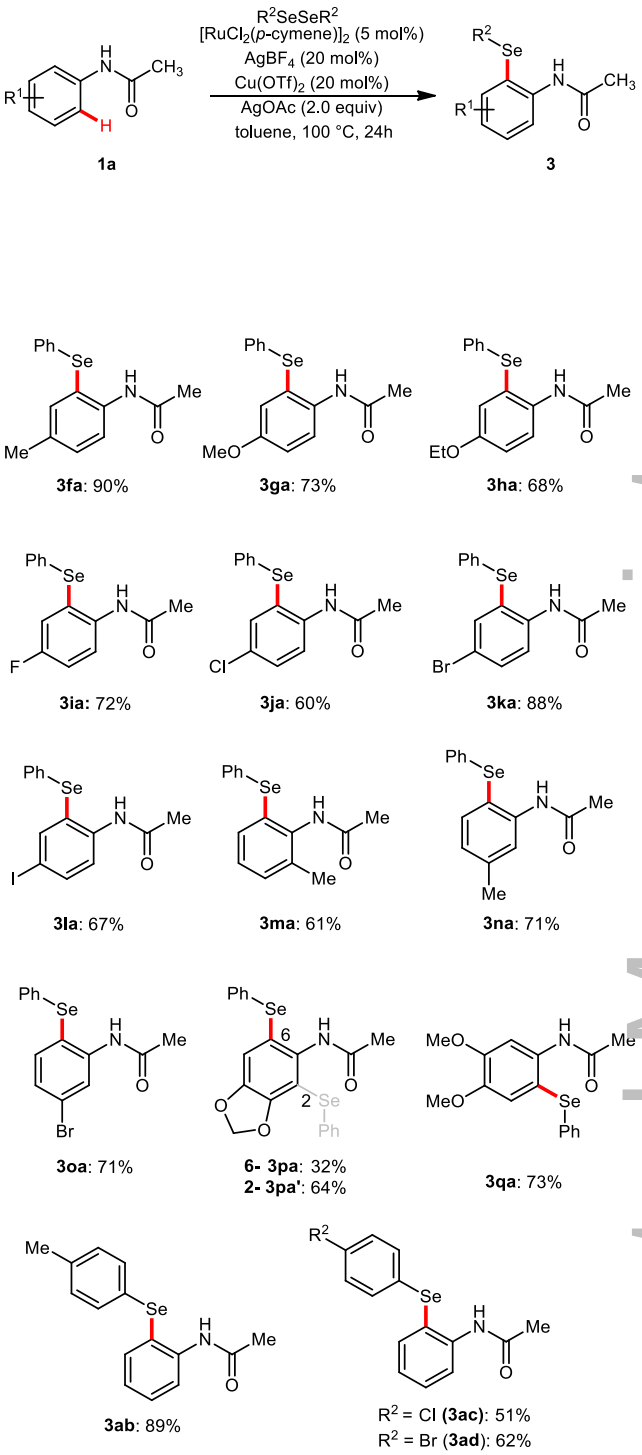


Scheme 2. Effect exerted by the *N*-substituent

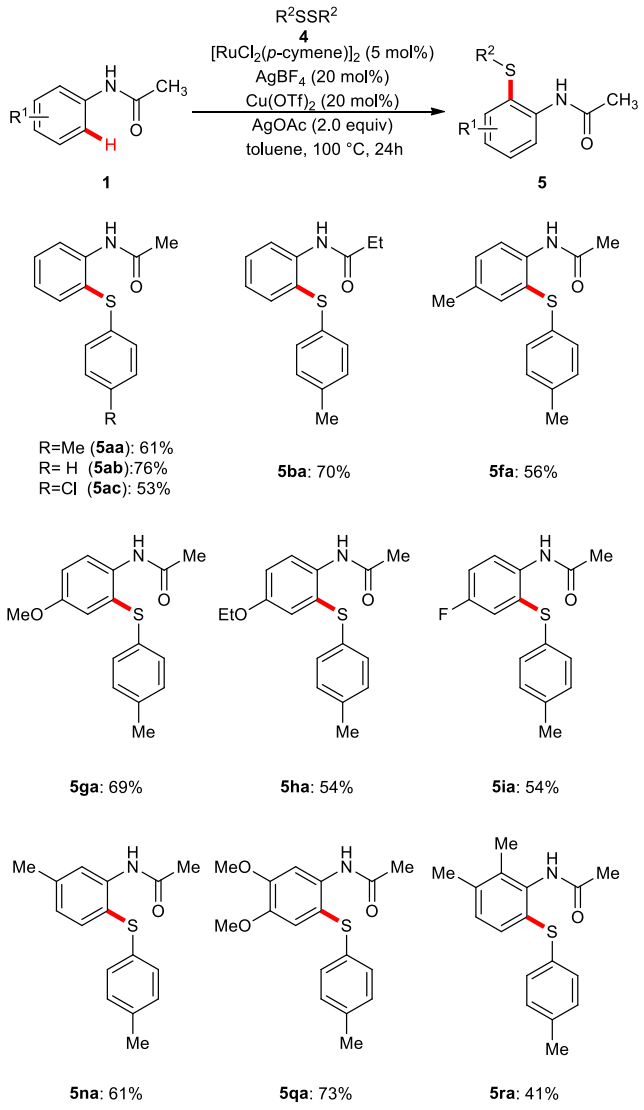
With the optimized reaction conditions in hand, we probed the versatility of the C−H selenylation with respect to the differently substituted anilide **1** (Scheme 3). Substrates bearing electron-rich and electron-deficient groups on the *para* position reacted with 1,2-diphenyldiselane **2a** smoothly with excellent positional selectivity, while electron-rich substrates showed better reactivity (**3fa**-**3ha**). Importantly, useful functional groups, such as chloro, bromo and iodo were well tolerated under the ruthenium catalysis regime, which could provide a versatile synthetic handle for further functionalization of the thus obtained products. It is noteworthy that the *N*-(4-ethoxyphenyl)acetamide (**1h**), a typical NSAID, proved to be a suitable substrate as well, delivering the pharmaceutically and synthetically useful **3ha**. The *ortho*-substituted substrate **1m** also reacted efficiently, and gave the desired product in 61% isolated yield. The site-selectivity of the C–H functionalization with *meta*-substituted anilides (**1n**, **1o** and **1q**) was largely controlled by steric interactions, thus delivering the mono-selenylated products in 71% (**3na**), 70% (**3oa**) and 73% (**3qa**) yields, respectively. In contrast, the substrate **1p** produced mono-selenylation on the more steric hindrance position as the main product. As anticipated, differently substituted diaryl disulfides showed high compatibility under the ruthenium catalysis manifold, furnishing the desired products **3ab**-**3ad** with high levels of chemo and positional selectivity. The dibenzyl diselenide coupling partner was also tested in this reaction. However, even under harsher reaction conditions only trace amounts of the selenylated product was observed.



Scheme 3. Scope of the C−H selenylations of substituted anilides **1**

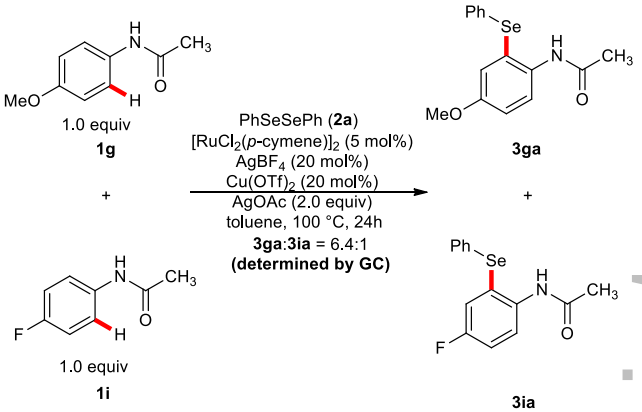
Encouraged by the viability of the approach for direct C−Se bond formation, we thereafter examined the use of diaryl disulfides (Scheme 4) in C−S bond formation under otherwise identical reaction conditions. Hence, the anilide **1** substituted with

either electron-attracting or electron-donating groups reacted with the diaryl disulfides **4** smoothly and gave the thiolated product **5** in good isolated yields. For the *meta*-substituted anilides, the ruthenium(II)-catalyzed C−H functionalization occurred at the less sterically hindered position to give the mono-thiolated products **5na** and **5qa**. The decorated diphenyl disulfides **4c** was also efficiently converted and gave the desired product with excellent levels of chemo selectivity.



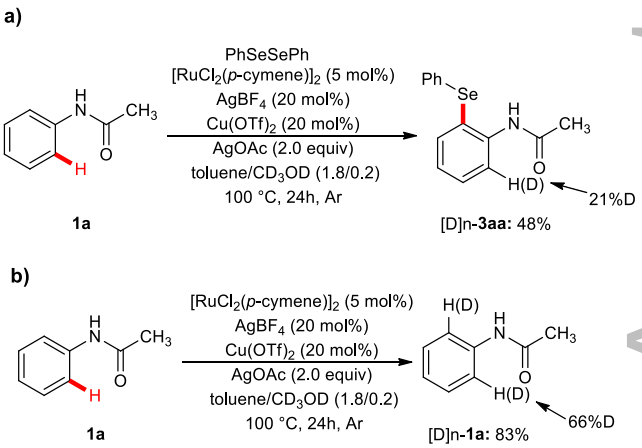
Scheme 4. C−H thionations of anilides **1**

Given the high catalytic activity of the versatile ruthenium(II) catalyst, we conducted mechanistic studies to unravel its mode of action. Intermolecular competition experiments between two differently substituted anilides showed that the electron-rich substrate **1g** was more reactive than the electron-deficient one **1i**, being hence indicative of a base-assisted internal electrophilic-type substitution (BIES) metalation event (Scheme 5). [19]



Scheme 5. Intermolecular competition between different substituted anilides **1**

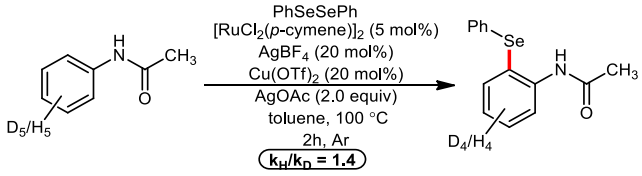
To further understand the reaction mechanism, experiments were conducted with isotopically labeled CD_3OD as the additive. The results of the H/D scrambling on the re-isolated anilide substrate $[D]_n$-**1a** and the selenylated product $[D]_n$-**3aa** indicated that the facile C–H activation step is reversible in nature (Scheme 6).



Scheme 6. H/D exchange reaction with aniline **1a**

Furthermore, ruthenium-catalyzed C–H selenylation with the isotopically labeled substrate [D_5]-**1a** and the parent substrate **1a** revealed an intermolecular kinetic

isotope effect (KIE) of $k_H/k_D \approx 1.4$ in competition experiment (Scheme 7), being again suggestive of a BIES C–H metalation event.



Scheme 7. Kinetic isotope effect studies

Conclusion

In summary, we have developed a highly efficient C–H chalcogenation for the challenging preparation of selenylated and thiolated anilides though ruthenium(II)-catalyzed C–H activation. A wide range of substrates could be employed for the versatile C–H functionalization, setting the stage for the C–H selenylations and thiolations with excellent chemo- and positional-selectivity as well as high functional group tolerance. The C–H activation strategy provides step-economical access to diversely decorated anilides through facile BIES C–H cleavage. Given the outstanding biological activities of selectively substituted anilides, the positional selective C–H functionalizations should prove instrumental for medicinal chemistry and drug discovery. Detailed studies on the reaction mechanism, the pharmacological evaluation of the thus obtained decorated anilides and further development of direct chalcogenations are ongoing in our laboratories, and will be reported in due course.

Experimental Section

Representative Procedure A: Ruthenium(II)-Catalyzed C–H Selenylation with Substituted *N*-phenylacetamide 1:
A suspension of *N*-phenylacetamide (**1a**) (34.2 mg, 0.25 mmol), 1,2-diphenyldiselane (**2a**) (157 mg, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.6 mg, 5.0 mol%), $AgBF_4$ (10.0 mg, 20 mol%), $Cu(OTf)_2$ (19 mg, 20 mol%) and AgOAc (83 mg 2.0 equiv) in toluene (2.0 mL) was stirred under argon at 100 °C for 24 h. At ambient temperature, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc: 4/1→2/1) to yield **3aa** (67 mg, 91%) as a brown solid. M. p = 78–80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.30 (d, J = 8.1 Hz, 1H), 8.06 (s, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.37–7.32 (m, 1H), 7.15 (s, 5H), 6.99 (td, J = 7.6, 1.2 Hz, 1H), 1.95 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.3, 139.6, 137.5, 130.9, 130.7, 129.9, 129.6, 127.0, 124.7, 121.0, 118.3, 24.7. HR-MS(ESI) *m/z* calcd for: $C_{14}H_{14}NOSe^+$ [M+H$^+$] 292.0235 found 292.0230.

Representative Procedure B: Ruthenium(II)-Catalyzed C–H Thiolation with Substituted *N*-phenylacetamide 1:
A suspension of *N*-phenylacetamide (**1a**) (33.8 mg, 0.25 mmol), 1,2-diphenyldisulfane (**4b**) (109 mg, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (7.6 mg, 5.0 mol%), $AgBF_4$ (10.0 mg, 20 mol%), $Cu(OTf)_2$ (19 mg, 20 mol%) and AgOAc (83 mg 2.0 equiv) in toluene (2.0 mL) was stirred under argon at 100 °C for 24 h. At ambient temperature, the reaction mixture was diluted with H_2O (10 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the crude product was purified by column chromatography on silica gel (Hexane/EtOAc: 4/1→2/1) to yield **5ab** (46 mg, 76%) as a brown solid. M. p = 88–90 °C. ^{1}H NMR (600 MHz) δ = 8.43 (d, J = 8.2 Hz, 1H), 8.20 (s, 1H), 7.57 (dd, J = 10.9, 4.9 Hz, 1H), 7.47–7.41 (m, 1H), 7.25–7.22 (m, 2H), 7.17 (t, J = 7.4 Hz, 1H), 7.13–7.10 (m, 1H), 7.08 (d, J = 7.5 Hz, 2H), 2.04 (s, 3H). ^{13}C NMR (150 MHz) δ = 168.5, 140.0, 136.5, 135.8, 131.0, 129.4, 127.3, 126.4, 124.5, 121.0, 120.0, 24.9. HR-MS (ESI) *m/z* calcd for: $C_{14}H_{14}NOS^+$ [M+H$^+$] 244.0791 found 244.0790.

Acknowledgements

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FULL PAPER

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