Division of Multidisciplinary Chemistry
– Interdisciplinary Chemistry for Innovation –

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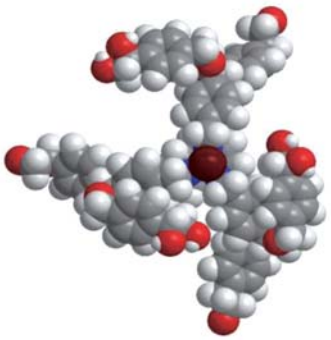
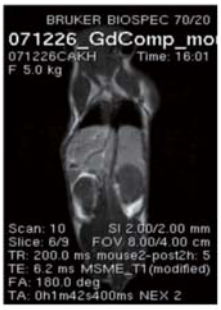
Scope of Research

Organic chemistry can contribute to the innovation through the design and synthesis of molecules those are valuable to human society. Our methodology possesses advantage in heteroatom chemistry, transition metalcatalyzed reactions, and asymmetric synthesis. As for the synthetic procedure, we take note to develop atomeconomic as well as environment-benign reactions. We recognize the importance of the collaboration with various fields of technology of industry and academia. Recent examples of our projects include design, synthesis, and evaluation of aromatic compounds used in light-emitting field-effect transistors, sugar-fullerene linked compounds used in photodynamic therapy of cancers, and gadolinium complex of chiral dendrimers used in magnetic resonance imaging of cancers (shown in the figure).





KEYWORDS

Innovation
Organic Synthesis
Heteroatom Chemistry
Transition Metal Catalyst
Asymmetric Synthesis

Selected Publications

Miyake, Y.; Kimura, Y.; Ishikawa, S.; Tsujita, H.; Miura, H.; Narazaki, M.; Matsuda, T.; Tabata, Y.; Yano, T.; Toshimitsu, A.; Kondo, T., Synthesis and Functional Evaluation of Chiral Dendrimer-Triamine-Coordinated Gd Complexes as Highly Sensitive MRI Contrast Agents, *Tetrahedron Lett*., **53,** 4580-4583(2012).

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Kondo, T.; Niimi, M.; Yoshida, Y.; Wada, K.; Mitsudo, T.; Kimira, Y.; Toshimitsu, A., Rhodium-catalyzed Linear Codimerization and Cycloaddition of Ketenes with Alkynes, *Molecules*, **15,** 4189-4200 (2010).

Sakanoue, T.; Yahiro, M.; Adachi, C.; Takimiya, K.; Toshimitsu, A., Electrical Characteristics of Single-component Ambipolar Organic Field-effect Transistors and Effects of Air Exposure of Them, *J. Appl. Phys*., **103,** [094509-1]-[094509-6] (2008).

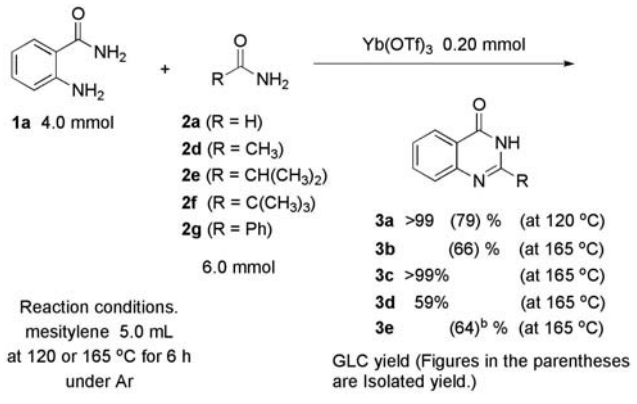
Sakanoue, T.; Yahiro, M.; Adachi, C.; Uchiuzou, H.; Takahashi, T.; Toshimitsu, A., Ambipolar Light-emitting Organic Field-effect Transistors Using a Wide-band-gap Blue-emitting Small Molecule, *Appl. Phys. Lett*., **90,** [171118-1]- [171118-3] (2007).

Simple, Selective, and Practical Synthesis of 2-Substituted 4(3*H*)-Quinazolinones by $Yb(OTf)_3$-Catalyzed Condensation of 2-Aminobenzamide with Carboxamides

4(3*H*)-Quinazolinones belong to one of the most important classes of fused heterocyclic compounds with a wide range of biological activities; *e.g.*, protein tyrosine kinase inhibitor, cholecystokinin inhibitor, antimalarial, antibacterial, anti-fungal, antiviral, anti-HIV, anticancer, antiinflammatory, antiallergy, anticonvulsant, antihypertensive, and antidiabetic. In addition, the 4(3*H*)-quinazolinone nucleus is also the key component of chromophoric, thermochromic, and fluorescent materials.

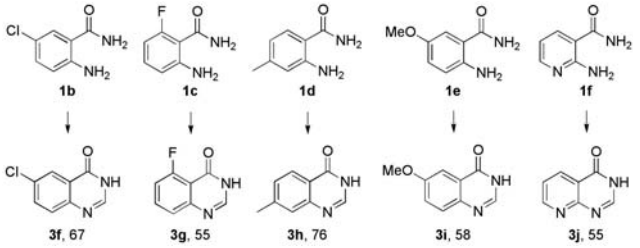
We found that the reaction of 2-aminobenzamide **1a** (4.0 mmol) with formamide **2a** (6.0 mmol) in the presence of a catalytic amount of $Yb(OTf)_3$ (0.20 mmol) in mesitylene (5 ml) at 120 ºC for 6 h affords 4(3*H*)-quinazolinone **3a** in quantitative yield (Scheme 1).

Formamide **2a** is the most effective C1 source in the construction of 4(3*H*)-quinazolinone **3a**, while methyl formate **2b** or paraformaldehyde, $(CH_2O)_n$ **2c**, instead of formamide **2a**, gave **3a** in 39% and 12% yield, respectively, even under reflux in mesitylene (bath temp. 165 ºC). Besides formamide **2a**, carboxamides, such as acetamide **2d**, 2-methylpropanamide **2e**, pivalamide **2f**, and benzamide **2g**, can be used in the present reaction to give 2-methyl-, 2-isopropyl-, 2-(*tert*-butyl)-, and 2-phenyl-4(3*H*)-quinozolinone (**3b-e**) in good to high yields as also shown in Scheme 1.



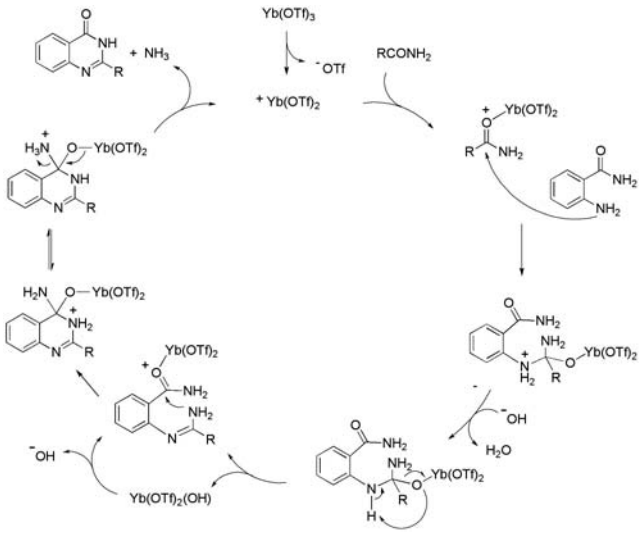
Scheme 1. $Yb(OTf)_3$-catalyzed synthesis of 4(3*H*)-quinazolinones **3** from 2-aminobenzamide **1a** and carboxamides **2**.

Condensation of several 2-aminobenzamides (**1b-e**) with formamide (**2a**) proceeded smoothly, by $Yb(OTf)_3$ catalyst, to give the corresponding 4(3*H*)-quinazolinones (**3f-i**) in moderate to high isolated yields (Scheme 2). In addition, the related 2-aminonicotinamide (**1f**) also reacted with **2a** under the present catalytic reaction conditions to give pyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**3j**) in an isolated yield of 55%.



Scheme 2. Synthesis of 4(3*H*)-quinazolinones **3f-j** by $Yb(OTf)_3$-catalyzed condensation of 2-aminobenzamides **1b-e** and the related **1f** with formamide **2a**. Reaction conditions; **1** (4.0 mmol), $HCONH_2$ **2a** (6.0 mmol), $Yb(OTf)_3$ (0.20 mmol) in mesitylene (5.0 mL) at 165 °C (bath temp.) for 6 h under an Ar atmosphere.

Considering the results obtained above, the most plausible mechanism is illustrated in Scheme 3. We believe that the dissociation of a triflate anion (OTf^-) from $Yb(OTf)_3$ first occurred to generate catalytically active $Yb(OTf)_2^+$, which immediately coordinates to a carbonyl oxygen in carboxamide. Subsequent nucleophilic attack of an amino group in 2-aminobenzamide to the activated carbonyl carbon in carboxamide proceeded to give an amidine intermediate and $Yb(OTf)_2(OH)$, followed by dissociation of OH^- to regenerate $Yb(OTf)_2^+$. $Yb(OTf)_2^+$ again coordinates to a carbonyl oxygen in benzamide to promote the intramolecular nucleophilic attack of an amino group to the activated carbonyl carbon. Isomerization of the intermediate, followed by elimination of NH_3 give 4(3*H*)-quinazolinone and $Yb(OTf)_2^+$.



Scheme 3. The most plausible mechanism of this reaction.