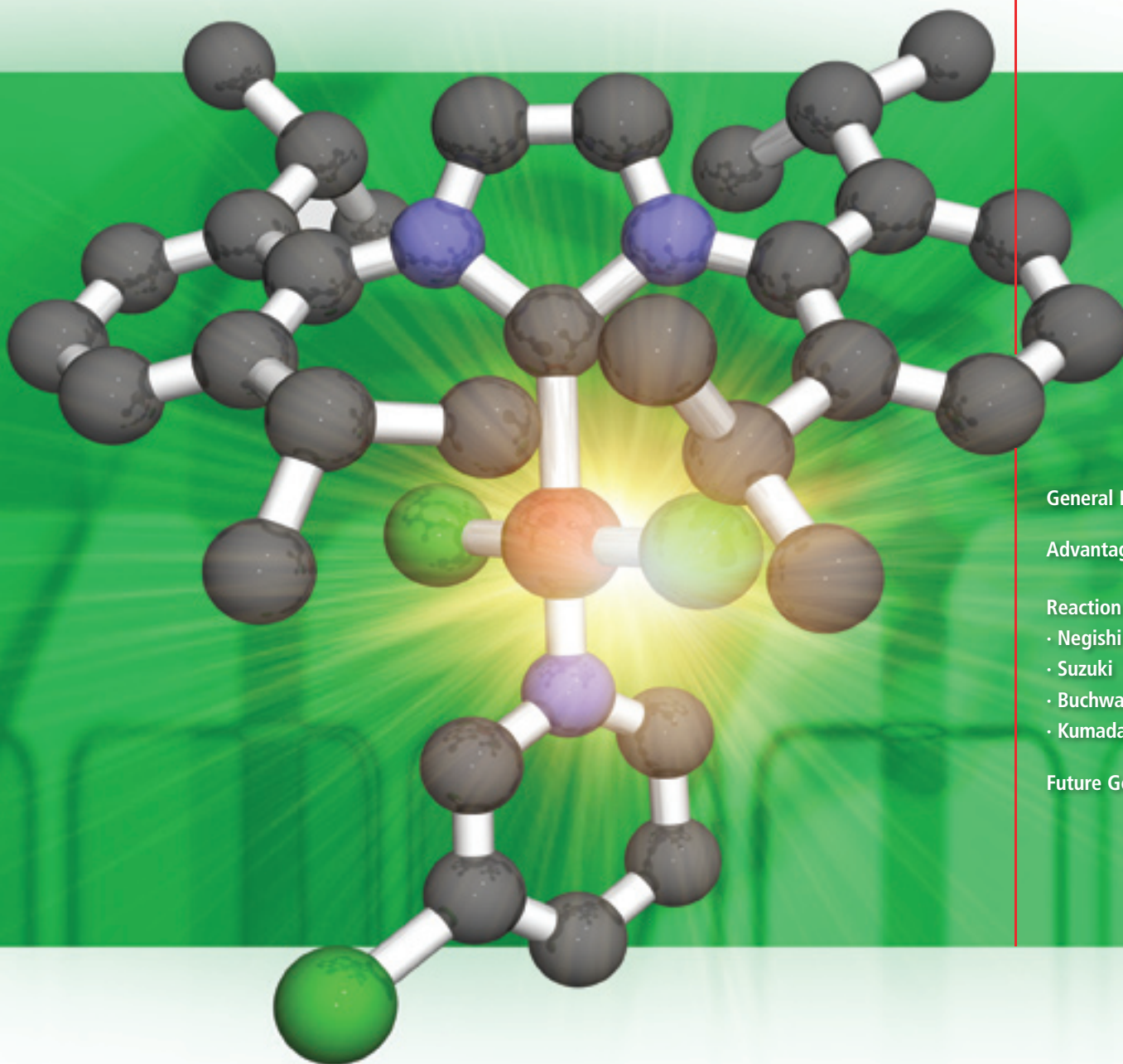


**新しい Pd 触媒
PEPPSI™ Catalyst**



General Background

Advantages of PEPPSI™

Reaction Types

- Negishi
- Suzuki
- Buchwald–Hartwig
- Kumada

Future Generation PEPPSI™

はじめに

Pd(PPh₃)₄の触媒作用が Malatesta, Angoletta らによって見出されて以来¹、パラジウム及びその錯体は、複雑な有機分子の効率的な触媒合成において中心的な役割を果たし、現在の有機合成化学において C-C 結合、C-O 結合、C-N 結合を形成するクロスカップリング反応に欠かせない存在となっています^{2,3}。クロスカップリング反応における触媒の開発は、ホスフィン配位子を含む錯体の設計と応用を中心に行われてきました。パラジウム触媒にホスフィン配位子を用いることには、コスト、安定性、前駆体の市販試薬の不足などの多くの欠点があります。たとえば Pd(PPh₃)₄ は触媒反応に幅広く適用されていますが、保存安定性が低く窒素下で取り扱う必要があります。しかしながら、多くの基質や反応系に対して Pd(PPh₃)₄ を上回る活性を示す触媒がほとんど報告されていないのが現状です。

安定で高活性な新規 Pd 触媒 PEPPSI™

これらの欠点を克服するため、ヨーク大学の Mike Organ 教授らによってシンプルな概念をベースとして優れた含窒素ヘテロ環カルベン (NHC) Pd 錯体が考案されました⁵。かさ高い NHC 配位子 2,6-塩化イソプロピルフェニルイミダゾリウム (IPr) と σ 供与性 3-クロロピリジン配位子を PdCl₂ に反応させ安定性を高めたこの触媒は、Pyridine-Enhanced Precatalyst Preparation Stabilization and Initiation の頭文字をとって PEPPSI™ と名づけられました。3-クロロピリジン配位子は "throw-away" 配位子 ("使い捨て" の意) として機能し、かさ高い IPr 配位子は還元的脱離反応を促進して TON を向上します (Figure 1)⁶。NHC 配位子の高い σ 電子供与能により、従来のホスフィン配位子よりも強く金属と結合し、金属の解離を防ぎます。NHC 配位子の不飽和性は触媒活性には影響しませんが、触媒の安定性や形成しやすさに影響します。

Sigma-Aldrich は、Organ 教授の研究グループとの共同開発により、PEPPSI™-IPr 触媒を提供しています。C-C 結合、C-N 結合生成反応を効果的に触媒できること、堅牢性、安定性、比較的価格低価格であることから、試験研究及びファインケミカル分野での幅広い応用が期待されています。

触媒関連製品の一覧は、Web サイト sigma-aldrich.com/catalysis でご覧いただけます。またお探しの試薬が見つからない場合は、sialjpts@sial.com まで日本語でお気軽にご相談ください。皆様の研究開発を速やかに成功に導くため、Sigma-Aldrich は喜んでご協力します。

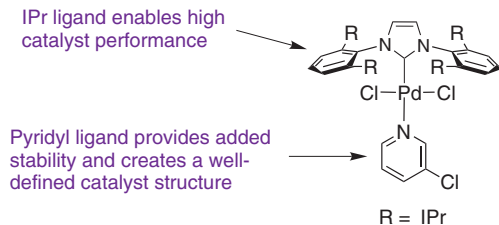


Figure 1

PEPPSI™-IPr の特徴

- 空気や水に対して極めて安定
- 従来の Pd 触媒よりも高い (もしくは同等の) 活性
- 種々の反応に利用可能
- 多くの反応は室温で進行
- その他の配位子は不要
- 低コスト
- バルク供給可能

About Our Cover

The cover illustration shows a rendering of the PEPPSI™-IPr catalyst X-ray structure. The 3-chloropyridine ligand bisects the *N*-heterocyclic carbene (NHC) ligand and lies roughly in the same plane as the ancillary chloride ligands, effectively granting the expected square planar geometry about the Pd(II) metal center. Please note that the hydrogens on the 2,6-isopropylphenyl-NHC and pyridyl ligands have been omitted for clarity.

Representative Example with PEPPSI™

Scheme 1 illustrates the strong ability of PEPPSI™ to effect cross-couplings (sp^2 - sp^2 Negishi) under mild reaction conditions. The aryl bromide was completely converted to 4-methyl-4'-methoxy-biphenyl in 2 h at room temperature, whereas competitive Pd systems require overnight reaction times to reach adequate conversions. Another compelling feature of the PEPPSI™ system is the low (1 mol %) loadings in Negishi couplings, wherein sp^3 - sp^3 couplings have been achieved in short (30 min) reaction times with high conversions. Previous NHC protocols involving alkyl-alkyl coupling reactions have not been accomplished successively in high yield.

PEPPSI™ Activation and Catalytic Cycle

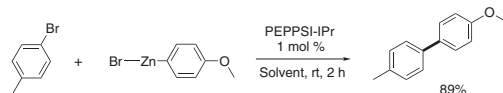
The challenges associated with improving palladium catalyst systems for cross-coupling are often related to the rate of active catalyst formation and subsequent stability throughout the catalytic cycle. In the case of PEPPSI™-IPr, rapid, quantitative conversion to product in Negishi couplings has been documented by the Organ group.⁶ In this catalyst system, activation most likely occurs via reduction of the Pd(II) center by the organometallic reagent, followed by pyridine dissociation from the newly formed Pd(0) species (**Scheme 2**). The yield of *n*-heptylbenzene under typical Negishi cross-coupling conditions is strongly dependent upon the structural environment around the Pd center. Isopropyl groups influence the conversion of cross-coupling product, which may imply a stabilizing influence on the PEPPSI™-IPr Pd(0) center versus NHC analogs **1a** and **1b** (**Table 1**). Thus, the bulky isopropyl NHC ligand accelerates the reductive elimination of *n*-heptylbenzene, while stabilizing the Pd center.

(1,3-Diisopropylimidazol-2-ylidene)(3-chloropyridyl) palladium(II) dichloride

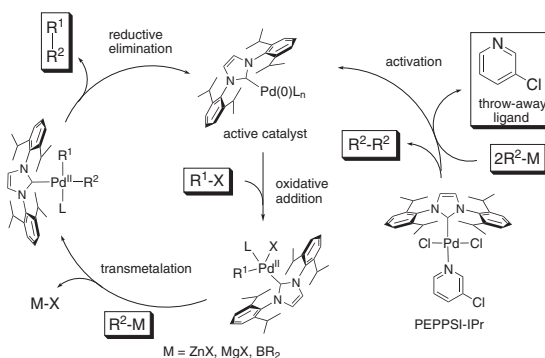
C₃₂H₄₁Cl₃N₃Pd

MW: 679.46

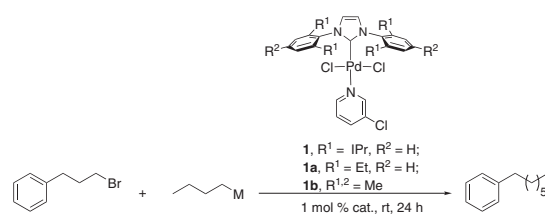
669032-1G	1 g	¥8,600
669032-5G	5 g	¥30,000



Scheme 1



Scheme 2



entry	M	yield of <i>n</i> -heptylbenzene
1	ZnBr	100% (1), 34% (1a), 8.0% (1b)
2	BBu ₂	100% (1), 31% (1a), 6.5% (1b)

Table 1

Cheminars™

Sigma-Aldrich's New Web-Based
Chemistry Seminars

オンラインセミナー Cheminars™

- ・有機合成の最新の技術情報、新製品情報を Web 上で公開
- ・PC からいつでもアクセス可能
- ・約 3 ヶ月ごとの 新トピックス

www.sigma-aldrich.com/cheminars をご覧ください！
(Flash 8 Player が必要です)

バルク供給/スケールアップのご相談は…

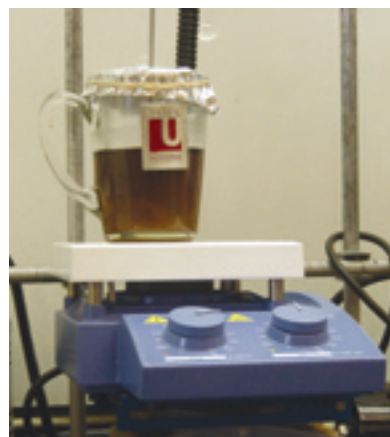
ファインケミカル事業部 Tel:03-5796-7340 Fax:03-5796-7345 E-mail:sialjpcf@sial.com

Advantages of the PEPPSI™-IPr Catalyst

- Extremely stable to air and moisture
- Commercialized on kilo scale
- Improved or comparable activity to known Pd catalysts
- High performance in various reaction paradigms
- Many reactions occur at room temperature
- No need for additional ligands → one-component catalyst
- Competitive pricing

Stability and Handling

Unlike traditional palladium phosphine and NHC catalysts, PEPPSI™ is robust and can be stored indefinitely outside an inert atmosphere. The catalyst may be weighed out on bench utilizing normal methods and can even be subjected to a water workup without observable decomposition by ¹H NMR. Perhaps most impressively, PEPPSI™ has been heated in dimethylsulfoxide at 120 °C for hours without decomposition and subsequent deactivation of the catalyst. This Pd(II) complex becomes active in situ through reduction to the Pd(0)-NHC active catalyst—thus it can be considered a ligand stabilized Pd(PPh₃)₄ alternative, minus the handling deficiencies. The picture above brilliantly illustrates the multi-gram synthesis and impressive stability of PEPPSI™-IPr in a coffee mug under atmospheric conditions!



Reaction Types

- Negishi Reactions
- Suzuki Reactions
- Buchwald-Hartwig Aminations
- Combined Amination/Heck Reaction
- Kumada Couplings
- Future Cross-Couplings

Negishi Couplings

Negishi reactions are comprised of the coupling between an alkyl halide with an alkyl organometallic reagent, which is unexplored territory for Pd-NHC complexes. The Organ group has achieved these difficult transformations with PEPPSI™-IPr and in the process has developed a general, efficient protocol with broad functional group tolerance.⁶ This PEPPSI™ catalyst satisfies two main criteria required for successful couplings: 1) the reaction should be conveniently run without the need for special handling, i.e., use of a glove box; 2) the catalyst system must be extended to a diverse spectrum of reaction partners.

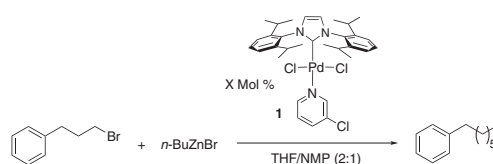
The success of this Pd-NHC catalyst system is highly dependent upon the activation of the Pd(0) catalyst, in part through the use of **LiCl/Br as an additive**. The Organ group attempted to perform a Negishi cross-coupling of *n*-butylzinc, as prepared by Hou and co-workers,⁷ with the requisite bromoalkane and only recovered starting material after stirring the reaction for hours at room temperature. They applied the same reaction conditions, but used *n*-butylzinc bromide prepared from the method of Hou along with 2 eq. of LiBr and found that the reaction produced the sp³-sp³ coupled organic in excellent yield in 30 min. Thus, the activation of the alkylzinc reagent, via the formation (presumed) of a lithium zincate, is an important driving force for the successful utilization of the PEPPSI™ catalyst in Negishi couplings.

PEPPSI™-IPr Loading

The Negishi reaction conditions utilizing PEPPSI™ have been optimized and are presented in **Table 2**. Note that catalyst loadings as low as 0.5 mol % show complete conversion to *n*-heptylbenzene within 3 h at room temperature.

PEPPSI™-IPr vs. in situ

The Organ group ran a direct comparison of PEPPSI™ versus an in situ generated NHC complex and found that the former system gave apparent TON h⁻¹ of 300 at 0.1 mol % loading, while the latter



Entry	X mol %	Yield (%)
1	4	100
2	2	100
3	1	100
4	0.5	100
5	0.1	63
6	1, 15 min	100

Table 2

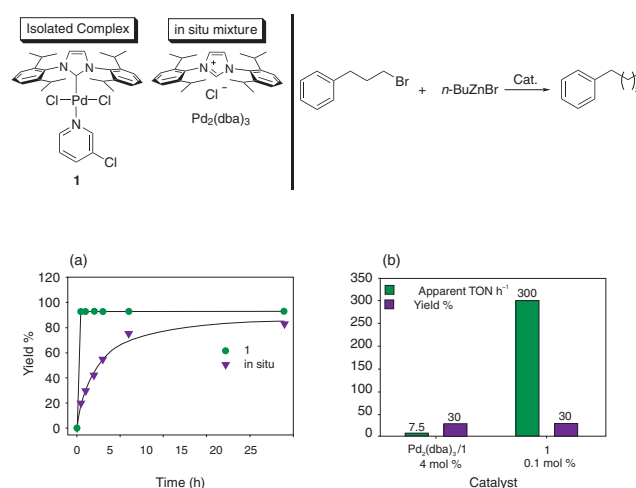


Figure 2

system afforded only 7.5 TON h⁻¹ at 4 mol % loading (**Figure 2**). It should be mentioned that it was not practical to measure the reaction rate of the isolated PEPPSI™ catalyst utilized in a coupling reaction at a loading of 1 mol %, because the rates were extremely fast. This comparison shows that only ca. 0.1 mol % of an active catalyst is formed at 1 h reaction time, even though 4 mol % of the precursors are used, when considering the apparent TONs and assuming that the same active species is generated in both cases. This study clearly proves the superiority of the preformed PEPPSI™ catalyst over the in situ methodology.

Organohalide Compatibility in the Negishi Reaction

Alkyl chlorides and sulfonates have effectively been coupled by adding 2 eq. of LiBr to the reaction mixture. Interestingly, alkyl chlorides and mesylates required a THF/NMP or THF/DMI ratio of 1:3 to achieve high product yields, whereas the corresponding alkyl bromides were coupled in high yields utilizing a solvent ratio of 2:1 (THF/NMP). These observations present the rare opportunity to selectively couple an alkyl bromide in the presence of an alkyl chloride, followed by an alkyl chloride coupling in a sequential fashion. **Table 3** illustrates the effectiveness of the PEPPSI™ catalyst system, wherein the cross-coupling of organochlorides and bromides, aryl triflates, and alkyl mesylates runs smoothly in all possible pairings. Catalyst **1** offers the widest substrate range performed successively in the Negishi reaction.

Experimental Conditions

Alkyl halide (1 eq.), alkylzinc bromide/chloride (1.6 eq.), PEPPSI™-IPr (1, 1 mol %), THF/NMP or THF/DMI, room temperature to 60 °C.

For all Negishi couplings the following workup procedure was used: after reaction completion, the solution was diluted with ether (~5 x volume) and washed successively with a 1 M Na₃EDTA solution (3 eq. of NaOH with EDTA), water, and brine. The combined organic solution was dried with MgSO₄, filtered through a sintered funnel, the solvent removed in vacuo, and the residue purified by flash chromatography.

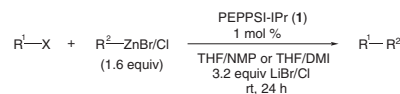
Representative Experimental Procedures and Results

Negishi Substrate Scope: sp³-sp³ couplings

sp³-sp³ couplings, **Scheme 3**: a scintal vial was charged with **1** (0.034 g, 1 mol %) and a stir bar in air. Under an inert atmosphere LiBr (0.139 g, 0.8 mmol) was added followed by a septum. The vial was purged with argon after which THF (0.8 mL) and DMI (0.8 mL) or NMP (0.8 mL) were added and the mixture stirred until the solids dissolved. After this time, the organozinc (0.8 mL, 1.0 M in DMI or NMP, 0.8 mmol) and the organohalide or pseudohalide (0.5 mmol) were added. The septum was replaced with a Teflon®-lined cap under a N₂ flow and the reaction stirred for 2h, followed by workup (cf. above).

PEPPSI™-IPr (**1**) is a highly efficient and mild catalyst for forming alkyl-alkyl bonds, as illustrated in **Figure 3**. Sp³(RX)-sp³(RZnX) couplings mediated by **1** include a wide spectrum of functionality such as esters, nitriles, and amides (**2-5**). Notably the terminal alkynyl TMS group in compound **7** is completely stable to the cross-coupling of an alkyl chloride under room temperature reaction conditions.

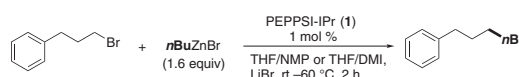
These results lend credence to the possibility of coupling substrates that contain biologically active components and subsequent expeditious synthesis of natural product intermediates. The wide range of alkyl bromides, chlorides, and tosylates supported by the PEPPSI™ system extend the general usefulness (compounds **2-7**) of this reaction paradigm. Incredibly, the Organ research group successfully achieved the coupling of a bromide in the presence of a chloride by judicious choice of reaction conditions (compound **2**).



Entry	R ¹	X	R ²	Yield [%] ^a
1	Ph(CH ₂) ₃	Cl	<i>n</i> Bu ^b	88
2	Ph(CH ₂) ₃	OMs	<i>n</i> Bu ^c	100
3	Ph	Cl	<i>n</i> Heptyl ^d	100
4	Ph	Br	<i>n</i> Heptyl ^b	100
5	Ph	OTf	<i>n</i> Heptyl ^d	100
6	<i>n</i> Heptyl	Br	Ph ^e	100
7	<i>p</i> Tolyl	Cl	<i>p</i> MeOC ₆ H ₄ ^e	80
8	<i>p</i> Tolyl	OTf	<i>p</i> MeOC ₆ H ₄ ^e	71

^a GC yield against calibrated undecane internal standard performed in duplicate. ^b THF/DMI, 2:1. ^c THF/DMI, 1:3. ^d THF/DMI, 1:2. ^e THF:NMP, 2:1, no LiCl/Br.

Table 3



Scheme 3

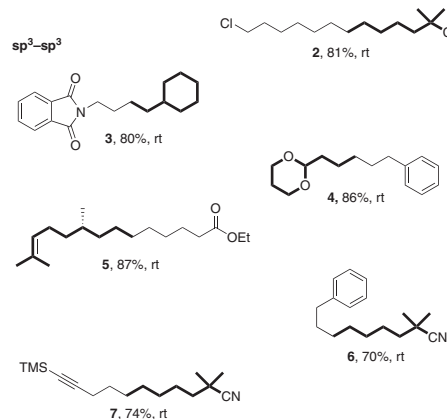
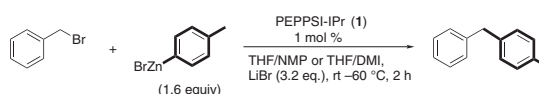


Figure 3



Scheme 4

Negishi Substrate Scope: sp^3 - sp^2 couplings

sp^3 - sp^2 couplings, **Scheme 4**: A vial was charged with **1** (0.034 g, 1 mol %) in the air and under an N_2 atmosphere $ZnCl_2$ (0.107 g, 0.8 mmol) and a stirbar were added. The vial was capped with a rubber septum and then purged with argon. THF (0.8 mL) was added along with the required Grignard-type reagent (0.8 mL, 1.0 M in THF, 0.8 mmol) and the mixture stirred until a white precipitate formed. Under an N_2 atmosphere, LiBr (0.139 g, 1.6 mmol), DMI (0.8 mL), or NMP (0.8 mL), and the organohalide or pseudohalide (0.5 mmol) were added. The septum was replaced with a Teflon[®]-lined cap under a N_2 flow and the reaction stirred for 2 h, followed by workup conditions (cf. above).

The range of substrates successively applied in the Negishi reaction for sp^3 (RX)- sp^2 (RZnX) couplings includes both electron-donating and electron-withdrawing substituents on the arylzinc reaction partner (**Figure 4**). Note the coupling of chiral (*S*)-citronellyl bromide, in which the final product shows no observable erosion of enantiopurity (compound **8**). The mild nature of the PEPPSI[™] catalyst tolerates pendant alkenyl and alkynyl functional groups as well as the often sensitive TMS group (**8–10**). Isolated product yields in this coupling class are all greater than 80%.

Negishi Substrate Scope: sp^2 - sp^3 couplings

sp^2 - sp^3 couplings, **Scheme 5**: A scintal vial was charged with **1** (0.034 g, 1 mol %) and a stir bar in air. Under an inert atmosphere, LiBr (0.139 g, 0.8 mmol) was added followed by a septum. The vial was purged with argon after which THF (0.8 mL) and DMI (0.8 mL) or NMP (0.8 mL) were added and the mixture stirred until the solids dissolved. After this time, the organozinc (0.8 mL, 1.0 M in DMI or NMP, 0.8 mmol) and the organohalide or pseudo halide (0.5 mmol) were added. The septum was replaced with a Teflon[®]-lined cap under a N_2 flow and the reaction stirred for 2 h, followed by workup (cf. above).

PEPPSI[™]-IPr complex **1** is able to catalyze the coupling of aryl halides (or triflates) with alkylzinc reagents in high yield (**Figure 5**). Furthermore, all reactions studied displayed no obvious transmetalation to form arylzinc reagents. The mildness of the PEPPSI[™] system extends to the Negishi coupling of a chiral zinc reagent with an acyl chloride (**14**), wherein subsequent decarbonylation was not observed under the reaction conditions. Also heteroatom-containing substrates were carried forward with 100% fidelity, further demonstrating the benefits of this catalyst system to the synthetic community.

Negishi Substrate Scope: sp^2 - sp^2 couplings

sp^2 - sp^2 couplings, **Scheme 6**: A vial was charged with **1** (0.034 g, 1 mol %) in the air and then $ZnCl_2$ (0.107 g, 0.8 mmol) and a stirbar were added under an inert atmosphere. The vial was capped with a rubber septum and then purged with argon. THF (0.8 mL) was added along with the required Grignard-type reagent (0.8 mL, 1.0 M in THF, 0.8 mmol) and the mixture stirred until a white precipitate formed (ca. 15 min). Under an inert atmosphere, NMP (0.8 mL) and the organohalide or pseudohalide (0.5 mmol) were added. The septum was replaced with a Teflon[®]-lined cap under a N_2 flow and the reaction stirred for 2 h, followed by workup under the conditions described above.

The high activity of PEPPSI[™] catalyst **1** in Negishi couplings offers a distinct advantage for C-C bond-forming reactions in homogeneous catalysis. To this end, **1** holds great promise as a generally applicable catalyst for a wide variety of cross-coupling paradigms. The sp^2 - sp^2 couplings shown represent direct access to sterically hindered biaryls and heteroaromatic systems utilized as drug platforms in natural product synthesis (**Figure 6**). A diverse spectrum of electron-donating and -withdrawing partners utilized in these sp^2 - sp^2 couplings solidifies PEPPSI[™]'s claim as a more active catalyst in Negishi processes than related and well-studied Pd-phosphine systems.

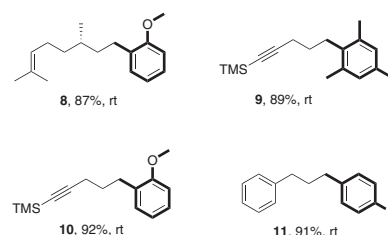
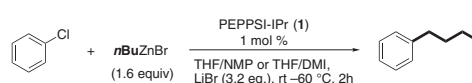


Figure 4



Scheme 5

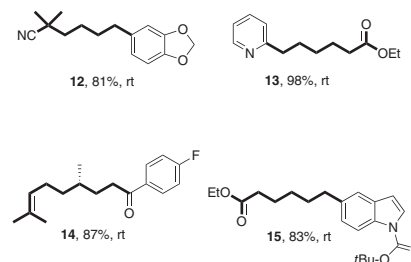
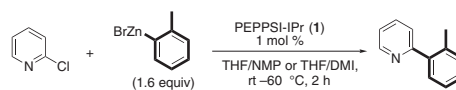


Figure 5



Scheme 6

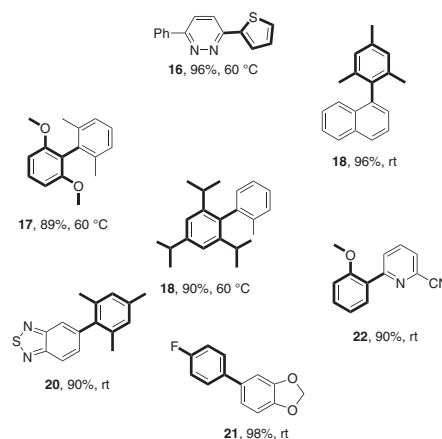


Figure 6

PEPPSI™-IPr Advantages in the Negishi Coupling

- No glove-box handling required
- Prototypical and advanced couplings possible
- Reactions performed at room temperature in a few hours
- Selectively activate a bromide over a chloride
- Diverse range of halides: Cl, Br, I, OTs, OMs, or OTf

Suzuki Couplings

Suzuki reactions involve the coupling of organoboron partners with alkyl, aryl, and alkenyl halides or triflates (**Scheme 7**).⁸ PEPPSI™ can be used effectively with a wide range of electron-rich (deactivated) and electron-poor (activated) substrates.⁹ The high activity of this catalyst system in the Suzuki coupling presents a strong case for application in industrial and academic research laboratories on a global scale.

All Suzuki reactions were accomplished using typical laboratory preparations without the need for glove-box handling. The PEPPSI™ precatalyst was weighed out in the air and activated in situ under a blanket of inert gas. The Organ group performed a full evaluation of heteroatom and electronically varied reaction partners. The reactions of various boronic acids proceeded smoothly in reagent-grade isopropanol and potassium *t*-butoxide was found to be the optimal base to ensure high product conversions. The broad utility of PEPPSI™-IPr was demonstrated in the production of a complex array of organic building blocks in high isolated yields (**Figure 7**, all via Method A).

Different procedures were utilized (Methods A–D, cf. below) that enabled the Organ group to expand the protocol to include potassium trifluoroborates by running the reaction in methanol. The flexibility of this catalyst system allows for the facile, rapid production of a wide array of drug intermediates, heteroaromatics, and bulky organic building blocks of varying electronic character (**Figure 8**). Furthermore, trialkylboranes are coupled with bromoalkanes in rapid fashion to yield the sp^3 - sp^3 coupled *n*-heptylbenzene product (**Scheme 8**).

Representative Experimental Procedures and Results

Procedure for Method A:

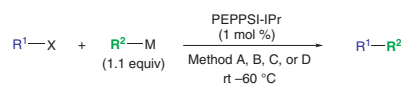
A vial was charged with potassium *tert*-butoxide (0.154 g, 1.30 mmol) and complex **1** (0.0068 g, 0.01 mmol) in the air, followed by purging with argon in triplicate. Tech. Grade isopropyl alcohol, 1.0 mL, was added via syringe and the solution was stirred at room temperature until a color change from yellow to red/brown was observed (ca. 10 min). The boronic acid (1.20 mmol) was added under an argon flow, the vial was then resealed followed by the organohalide (1.00 mmol) being added via syringe. The reaction was stirred at room temperature for the indicated time period and then diluted with diethyl ether (2 mL). After two additional 2-mL washings, the organic solution was dried with $MgSO_4$, filtered, concentrated, and purified by flash chromatography.

Procedure for Method B:

A vial was charged with complex **1** (0.0068 g, 0.01 mmol) in the air, K_2CO_3 (0.207 g, 1.50 mmol), the boronic acid (0.6 mmol) and the organohalide (0.5 mmol) followed by sealing with a septum and purging with argon in triplicate. Two milliliters of dioxane was added via syringe. The solution was stirred at 60 °C for the specified time period, and then diluted with diethyl ether (2 mL). After two additional 2-mL washings, the organic solution was dried with $MgSO_4$, filtered, concentrated, and purified by flash chromatography.

Procedure for Method C:

A vial was charged with complex **1** (0.0068 g, 0.01 mmol) in the air, K_2CO_3 (0.207 g, 1.50 mmol), the potassium trifluoroborate (0.55 mmol), and the organohalide (0.5 mmol), followed by sealing with a septum and purging with argon in triplicate. Tech. grade methanol, 2.0 mL, was added and the solution stirred at 60 °C for the specified time period, followed by dilution with diethyl ether (2 mL). After two additional 2-mL Et_2O washings, the organic solution was dried with $MgSO_4$, filtered, concentrated, and purified by flash chromatography.



Scheme 7

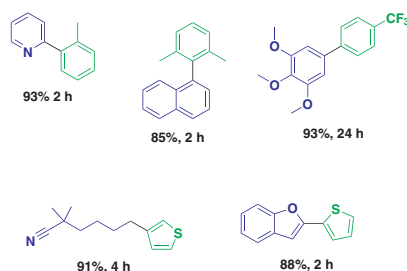


Figure 7

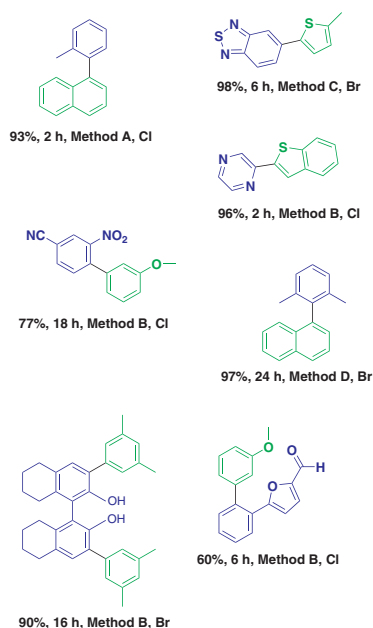
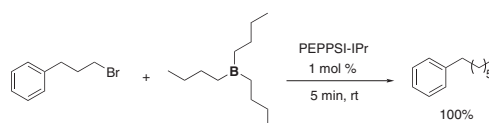


Figure 8



Scheme 8

Procedure for Method D:

Solid KOH (0.84 g, 1.50 mmol) was utilized instead of solid K_2CO_3 , otherwise Method B was utilized and the reaction carried forward at room temperature instead of 60 °C.

PEPPSI™-IPr Advantages in the Suzuki Coupling

- No glove-box handling
- Boronic acids, esters, and trifluoroborates well tolerated
- The halide can be Cl or Br
- Strong and mild bases have been applied successively
- Base sensitive substrates are acceptable

Buchwald–Hartwig Aminations

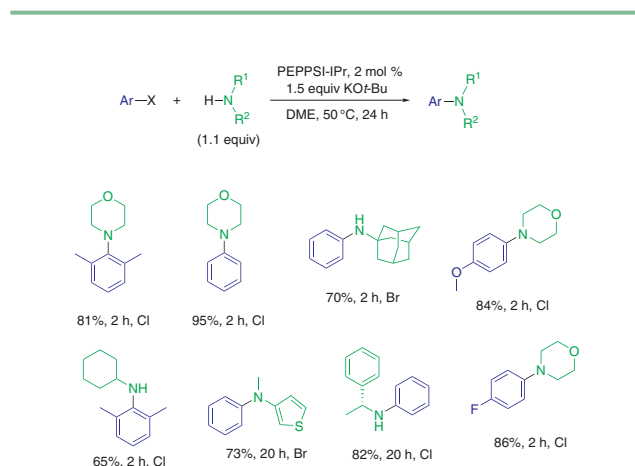
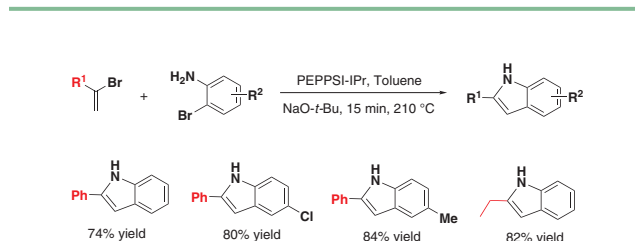
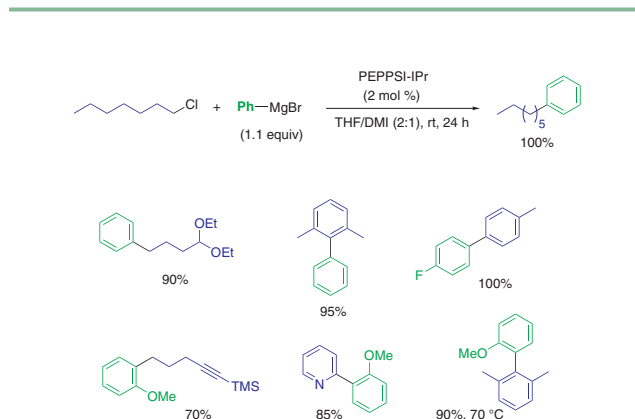
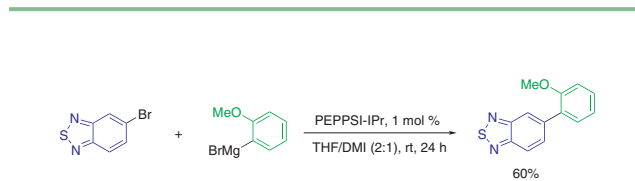
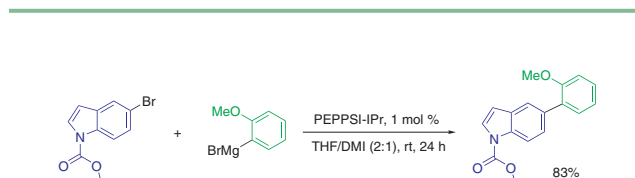
Since the work of Buchwald and others, palladium-catalyzed C–N bond-forming methodologies have traditionally focused on the use of (mostly) bulky, electron-rich phosphines as the ancillary ligands of choice.¹⁰ The Organ group was pleased to discover that PEPPSI™-IPr is an excellent catalyst for the palladium-catalyzed cross-coupling of aryl chlorides and bromides with amines.¹¹ The results in **Figure 9** indicate that use of this catalyst system allows for the successful arylation of various amines with superb yields. Morpholine, arylamines, and even adamantylamine undergo facile amination to afford a variety of aryl- and biarylamines. It is worth noting that the mild reaction conditions (temp. and base) tolerate electron-rich, electron-poor, and heteroaromatic substrates. This finding also shows that Pd–NHC complexes are not only viable as catalysts, but in many cases manifest tremendous efficiency and atom-economy in aromatic C–N bond-forming processes.

A new mild protocol expands the scope of homogeneous Pd C–N bond-forming catalysis even further. The indole moiety is one important element in organic compounds that exhibits pharmacological activity.¹² The most popular method utilized for indole synthesis is the Fischer indole synthesis, wherein an *N*-acyl hydrazone is transformed into the indole architecture through a sigmatropic rearrangement.¹³ As a complement to that well-known methodology, the Organ group has reacted a vinyl halide with various 2-bromoanilines in the presence of PEPPSI™ to afford 2-substituted indoles in good yields (**Figure 10**). This elegant strategy is being applied toward the expeditious preparation of *N*-alkyl and *N*-aryl indoles for combinatorial libraries.

Kumada Couplings

Many studies have been performed on the oxidative addition of aryl halides with Pd(0) and subsequent coupling of Grignard reagents. However, deficiencies in these previous examples include high catalyst loadings, high temperatures, and the necessity of aryl iodide substrates to reach adequate conversions.¹⁴ The Organ group has reported Kumada couplings of various aryl chlorides with Grignard reagents (**Figure 11**).¹⁵ These room-temperature oxidative additions of aryl chlorides equal the best results to date. Reactions with 1–2 mol % PEPPSI™-IPr in THF/DME (1:1) at room temperature produced the respective biaryl organics in excellent yields.

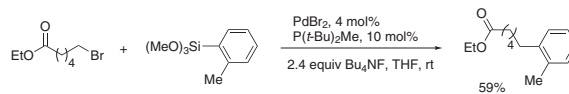
Note that both electron-rich and electron-poor Grignard reagents underwent reaction as well as sterically hindered aryl chlorides. This mild Kumada protocol shows superior tolerance of ether, TMS, and alkynyl functionalities. Heteroaromatic substrates undergo Kumada couplings in good yields at room-temperature and with low catalyst loadings (**Scheme 10**). Furthermore, functionalized 5-aryl-substituted indoles are produced in good yields (**Scheme 11**). The results shown in Figure 11 present a strong case for the wide acceptance of the PEPPSI™ catalyst for new discoveries in Kumada-type cross-couplings.

**Figure 9****Figure 10****Figure 11****Scheme 10****Scheme 11**

次世代のPEPPSI™ 触媒

ここ 10 年の間に、パラジウム触媒による芳香族ケイ素化合物と有機塩化物のクロスカップリング反応である檜山カップリング反応が開発されました¹⁶。有機ケイ素化合物は取り扱いが比較的容易でその多くが低毒性であるため、当然ながら合成化学において魅力的な基質です。Pd 触媒による檜山カップリング反応の多くは Csp^2-X タイプの求電子剤が中心ですが、Fu らは高活性 Pd 触媒系が臭化アルキルとのカップリングで高収率を与えると報告しました (Scheme 12)¹⁷。興味深いことに、Fu は、 $PdBr_2$ と塩化 2,6-ジメシチルフェニルイミダゾリウム (IMes) の存在下、臭化アルキルの直接アール化に利用できる高活性触媒が得られたと報告しています。これまでに示された PEPPSI™-IPr 触媒の優れた触媒作用にもとづいて、Organ らのグループはハロゲン化アルキルと有機ケイ素化合物の檜山クロスカップリング反応を検討しています。

パラジウム触媒によるアリル化合物の置換反応も、合成化学において期待されている炭素-炭素結合生成反応です。アリルアルコール、アリルエステルなどがよく用いられており、カルボン酸やオキシムなどの種々の基質と良好にカップリングします^{18,19}。このタイプの反応についても、PEPPSI™-IPr を用いた結果がヨーク大学の研究グループから報告される予定です。



Scheme 12

根岸カップリング、鈴木カップリング、熊田カップリングなどの各反応における結果が示すように、PEPPSI™触媒が sp^3-sp^3 、 sp^3-sp^2 、 sp^2-sp^2 カップリングに対して有用な触媒であるが示されました。反応性と実用性に優れた PEPPSI™は、天然物合成やバルクスケールでの製造に直接応用できる変換反応を触媒し、研究開発に貢献することでしょう。PEPPSI™-IPr の主な特徴は、触媒前駆体の空気中での安定性と、触媒サイクルへの迅速な活性化です。Pd (0) への還元において、IPr-NHC 配位子は独自の方法で金属中心を安定化すると同時に、還元的脱離反応を促進し TON を向上させます。Organ らのグループでは、PEPPSI™-IPr 触媒の工業用途での可能性を最大限に高めるため、新しい反応のパラダイムを開拓すべく研究を進めています。金属配位部位や NHC 構造を改良した錯体など、今後も新しい PEPPSI™触媒が続々と開発されることが期待されます。

References

- (1) (a) Malatesta, L. et al. *J. Chem. Soc.* **1957**, 1186. (b) Yamazaki, S. *Inorg. Chem.* **1982**, *21*, 1638. (c) Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374. (d) Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669. (e) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340.
- (2) (a) Hiyama, T., Hatanaka, Y. *J. Org. Chem.* **1988**, *53*, 918. (b) Tamao, K. et al. *J. Am. Chem. Soc.* **1972**, *94*, 4374. (c) Negishi, E. et al. *J. Org. Chem.* **1977**, *42*, 1821. (d) King, A. O. et al. *Chem. Commun.* 1977, 683. (e) Miyaura, N. et al. *Tetrahedron Lett.* **1979**, *20*, 3437. (f) Milstein, D. *J. Am. Chem. Soc.* **1978**, *100*, 3636.
- (3) Wolfe, J. P. et al. *J. Am. Chem. Soc.* **1996**, *118*, 7215.
- (4) (a) Frey, G. D. et al. *Organometallics* **2005**, *24*, 4416. (b) Herrmann, W. A. et al. *Angew. Chem., Int. Ed.* **2002**, *41*, 1363. (c) Viciu, M. S. et al. *Organometallics* **2004**, *23*, 1629. (d) Viciu, M. S. et al. *Org. Lett.* **2003**, *5*, 1479. (e) Jackstell, R. et al. *Angew. Chem., Int. Ed.* **2002**, *41*, 986. (f) Jensen, D. R. et al. *Angew. Chem., Int. Ed.* **2003**, *42*, 3810.
- (5) Organ, M. G. Rational Catalyst Design and its Application in sp^3-sp^3 Couplings. Presented at the 230th National Meeting of the American Chemical Society, Washington, DC, August 2005; Abstract 308.
- (6) Organ, M. G. et al. *Chemistry: A European Journal* **2006**, in press.
- (7) Hou, S. *Org. Lett.* **2003**, *5*, 423.
- (8) (a) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11. (b) Suzuki, A. J. *Organomet. Chem.* **1999**, *576*, 147.
- (9) Organ, M. G. et al. *Chemistry: A European Journal* **2006**, in press.
- (10) For lead references on the Pd-catalyzed coupling of amines with aryl halides, see: (a) Wolfe, J. P. et al. *Acc. Chem. Res.* **1998**, *12*, 805. (b) Hartwig, J. F. *Synlett* **1997**, 329. (c) Wolfe, J. P. et al. *J. Am. Chem. Soc.* **1996**, *118*, 7215. (d) Driver, M. S. et al. *J. Am. Chem. Soc.* **1996**, *118*, 7217.
- (11) Organ, M. G. et al. manuscript in preparation.
- (12) For background on the biological activity of indoles, see: Sundberg, R. J. *Indoles*; Academic Press: London, 1996, and references therein.
- (13) For a current review on the Fischer indole synthesis, see: Hughes, D. L. *Org. Prep. Proced. Int.* **1993**, *25*, 607.
- (14) Hassan, J. et al. *Chem. Rev.* **2002**, *102*, 1359.
- (15) Organ, M. G. et al. manuscript in preparation.
- (16) (a) Hiyama, T. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; Chapter 10. (b) Hiyama, T. et al. *J. Org. Chem.* **1988**, *53*, 918.
- (17) Fu, G. C. et al. *J. Am. Chem. Soc.* **2003**, *125*, 5616.
- (18) Kobayashi, S. *Org. Lett.* **2003**, *5*, 3241.
- (19) Takemoto, Y. et al. *J. Org. Chem.* **2005**, *70*, 5630.

バルク供給/スケールアップのご相談は…

ファインケミカル事業部 Tel:03-5796-7340 Fax:03-5796-7345 E-mail:sialjpcf@sial.com

Rieke® Organozincs

Custom Metal Reagents for Cross-Coupling

- Available as solutions in THF
- Diverse array of functional groups tolerated
- Industrially proven applications

Sigma-Aldrich では、Rieke® の有機亜鉛試薬を供給しております。

有機亜鉛試薬は、触媒分野で多くの報告がなされており、種々のクロスカップリング反応に利用されています¹。ヘテロ環化合物、芳香族フッ素化合物、その他電子特性の異なる種々の置換基を有する有機亜鉛化合物は、塩化アルキル・塩化アリールと良好な収率でカップリング生成物を与えます。

5-Chloro-2-thienylzinc bromide solution

$C_4H_2BrClS_2Zn$

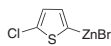
FW: 262.87

[312624-22-9]

497843-50ML

50 mL

¥18,000



5-Hexenylzinc bromide solution

$H_2C=CH(CH_2)_4ZnBr$

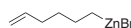
FW: 228.45

[226570-65-6]

498734-50ML

50 mL

¥20,800



(Cyclohexylmethyl)zinc bromide solution

$C_6H_{11}CH_2ZnBr$

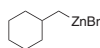
FW: 242.47

[135579-86-1]

498025-50ML

50 mL

¥17,200



Butylzinc bromide solution

$CH_3(CH_2)_3ZnBr$

FW: 202.41

[92273-73-9]

497746-50ML

50 mL

¥14,900



3,5-Dimethyl-1-adamantylzinc bromide solution

$C_{12}H_{19}BrZn$

FW: 308.57

[312692-99-2]

498432-50ML

50 mL

¥25,900



Phenylzinc bromide solution

C_6H_5ZnBr

FW: 222.4

[38111-44-3]

524719-50ML

50 mL

¥13,900



2,3,4,5,6-Pentafluorobenzylzinc chloride solution

$C_6F_5CH_2ZnCl$

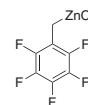
FW: 281.93

[308796-02-3]

499064-50ML

50 mL

¥22,600



2-Pyridylzinc bromide solution

C_5H_4BrNZn

FW: 222.39

[218777-23-2]

499382-50ML

50 mL

¥16,900



4-Fluorophenylzinc bromide solution

FC_6H_4ZnBr

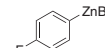
FW: 240.39

[181705-93-1]

498645-50ML

50 mL

¥15,200



(1)(a) Bunlaksanusorn, T. et al. *Angew. Chem. Int. Ed. Engl.* **2003**, 42, 3941. (b) Knochel, P. et al. *Chem. Rev.* **1993**, 93, 2117. (c) Chinchilla, R. et al. *Chem. Rev.* **2004**, 104, 2667.

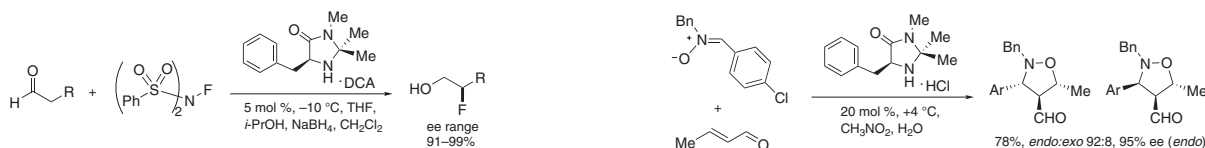
MacMillan Imidazolidinone OrganoCatalysts™

Metal-Free Asymmetric Catalysis

製品の特長

- 各種の反応における優れたエナンチオ選択性
- 高い触媒活性
- 官能基に対する汎用性
- 天然物合成における不斉 α -フッ素化

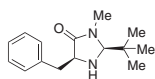
MacMillanらは、エナミンにより触媒されるアルデヒドの α 位の塩素化もしくは1,3-双極子付加環化など、様々なエナンチオ選択的な有機化学反応において要となるキラルなイミダゾリジノン有機分子触媒を開発しました。Sigma-Aldrichは、Materia社との共同開発により、迅速かつエナンチオ特異的にC-FもしくはC-H結合を形成可能な、6種のイミダゾリジノン有機分子触媒を提供しています。C-F形成反応としては、以下の例のように、少量(5 mol%)の触媒の添加により、アルデヒドの α 位を高エナンチオ選択的にフッ素化し、さまざまなアルコールが得られます。



References: (a) MacMillan, D. W. et al. *J. Am. Chem. Soc.* **2000**, 122, 9874. (b) MacMillan, D. W. et al. *J. Am. Chem. Soc.* **2005**, 127, 8826.

(2S,5S)-(-)-2-tert-Butyl-3-methyl-5-benzyl-4-imidazolidinone, 97% NEW

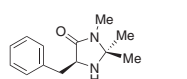
C₁₅H₂₂N₂O
FW: 246.35
[346440-54-8]



663107-500MG	500 mg	¥12,000
663107-1G	1 g	¥19,000

(5S)-2,2,3-Trimethyl-5-benzyl-4-imidazolidinone dichloroacetic acid NEW

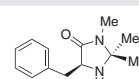
C₁₅H₂₀Cl₂N₂O₃
FW: 347.24



663085-500MG	500 mg	¥11,000
663085-2G	2 g	¥30,000

(5S)-2,2,3-trimethyl-5-phenylmethyl-4-imidazolidinone monohydrochloride, 97% NEW

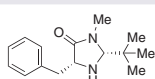
C₁₃H₁₈N₂O · HCl
FW: 254.76
[278173-23-2]



569763-500MG	500 mg	¥6,000
569763-2G	2 g	¥18,600

(2R,5R)-(-)-2-tert-Butyl-3-methyl-5-benzyl-4-imidazolidinone, 97% NEW

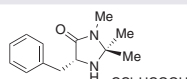
C₁₅H₂₂N₂O
FW: 246.35
[390766-89-9]



663093-500MG	500 mg	¥12,000
663093-1G	1 g	¥19,000

(5R)-2,2,3-Trimethyl-5-benzyl-4-imidazolidinone dichloroacetic acid NEW

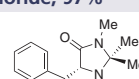
C₁₅H₂₀Cl₂N₂O₃
FW: 347.24



663077-500MG	500 mg	¥11,000
663077-2G	2 g	¥30,000

(5R)-2,2,3-trimethyl-5-phenylmethyl-4-imidazolidinone monohydrochloride, 97% NEW

C₁₃H₁₈N₂O · HCl
FW: 254.76
[323196-43-6]



663069-500MG	500 mg	¥6,000
663069-2G	2 g	¥16,000

For more information, please visit us at sigma-aldrich.com/catalysis.

Sigma-Aldrich 新サーチエンジンのご紹介

(<http://www.sigmaaldrich.com/>)

さまざまな Key Word や...



Substructure を選んで
構造式から



必要な試薬をお探しいただけます

MSDS、ロット試験成績表、NMR/IRスペクトル、国内在庫状況、価格を公開!



ぜひご利用下さい!

ご不明な点はテクニカルサポートまでどうぞ!



SIGMA-ALDRICH

シグマ アルドリッチ ジャパン株式会社

〒140-0002 東京都品川区東品川2-2-24 天王洲セントラルタワー4F

製品に関するお問い合わせは、弊社テクニカルサポートへ

TEL:03-5796-7330 FAX:03-5796-7335

E-mail : sialjpts@sial.com

在庫照会・ご注文方法に関するお問い合わせは、弊社カスタマーサービスへ

TEL:03-5796-7320 FAX:03-5796-7325

<http://www.sigma-aldrich.com/japan>

お問い合わせは下記代理店へ