

C–H Activation

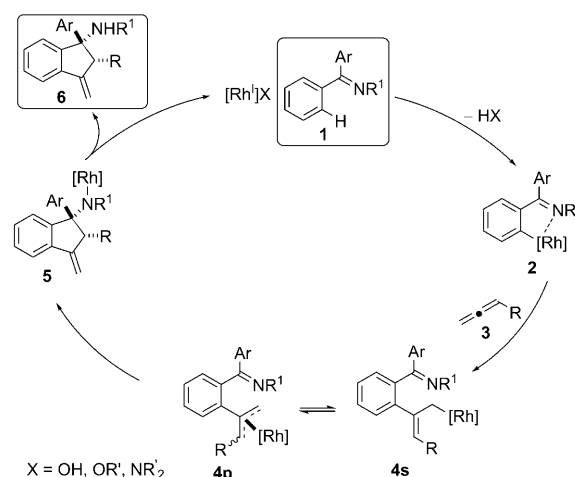
syn*-Selective Rhodium(I)-Catalyzed Allylations of Ketimines Proceeding through a Directed C–H Activation/Allene Addition Sequence*

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The transition-metal-catalyzed direct functionalization of C_{aryl}–H bonds is a rapidly growing field in organic chemistry that enables efficient access to a broad variety of building blocks.^[1] Nitrogen-containing directing groups such as pyridines, oxazolines, and imines play a pivotal role in the development of directed metal-catalyzed C–H functionalization reactions.^[2] In most of these reactions, the directing group itself is not modified during the transformation. Incorporating them into the reaction provides an additional handle to increase the diversity and molecular complexity of the formed products. However, organometallic species generated by initial C–H activation processes seem to have a poor nucleophilic character and more often participation of the imine directing groups involves reductive elimination to form C–N bonds rather than C–C bonds through addition to the imine. For example, Satoh and Miura reported rhodium(III)-catalyzed activation/cyclization processes of benzoic acids and alkynes to give isocoumarins.^[3] Furthermore, the groups of Jun, Fagnou, and Miura independently developed related syntheses of isoquinolines from imines and alkynes.^[4] In contrast, Kuninobu, Takai, and co-workers disclosed rhodium-catalyzed intermolecular [3+2] annulations of aromatic ketimines and unsaturated acceptors involving the nucleophilic addition of the generated rhodium species to the imine moiety.^[5] However, the harsh reaction conditions most often cause an elimination and loss of the amine functionality. Very recently, Zhao and co-workers developed related rhodium(I)-catalyzed cyclizations of unsubstituted ketimines and alkynes wherein the primary amine functionality was preserved.^[6]

Allyl metals obtained by hydrometalation of allenes are known to be highly efficient transient species for carbonyl allylation reactions.^[7] Despite their apparent synthetic utility, related reactions induced by carbometalation of allenes have not been used for such purposes. Herein, we report rho-

dium(I)-catalyzed [3+2] cyclizations of unsubstituted ketimines and terminal allenes to form methylene dihydroindolamines, and outline their potential for valuable regio-, diastereo-, and enantioselective C–H bond functionalizations.^[8] In particular, the methylene group and the free primary amine of the formed products are both amenable for additional functionalization, and represent a handle for designing domino processes. The envisioned reactivity is initiated by a cyclometalation of the imine **1** with a rhodium(I) complex that proceeds either by an oxidative addition and reductive elimination of HX (X = OH, OR, NR₂), or by a σ -bond metathesis which is essential for removal of the hydrogen atom from the rhodium center (Scheme 1).^[9]



Scheme 1. Rhodium(I)-catalyzed C–H functionalization/cyclization of ketimines **1** with terminal allenes.

In turn a carborhodation of the terminal double bond of an allene would lead to an allyl rhodium species either as its σ - (**4s**) or π -bound (**4p**) complex.^[10] Given the characteristics of the allyl rhodium(I) species,^[11] we speculated that they could participate in a stereochemically well-defined nucleophilic allylation of the imine moiety. The formed rhodium amido complex **5** could subsequently release product **6** upon protonation and regenerate the catalyst.

The reaction was initially developed with bis(*para*-tolyl)-methanimine (**1a**) and octa-1,2-diene (**3a**) as the prototype substrate combination (Table 1). Unsubstituted ketimines (R¹ = H) proved to be critical for the envisioned reactivity.^[12] A screening of different rhodium(I) precatalysts revealed that rhodium complexes bearing anionic oxygen-based ligands, such as hydroxide or acetate, promoted the transformation better than the [Rh(OMe)(cod)]₂ precatalyst that resulted in

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Table 1: Optimization of the C–H activation/cyclization sequence.^[a]

Entry	[Rh ^I]	L	Yield [%] ^[b]
1	[{Rh(cod)(OH)} ₂]	PPh ₃	0
2	[{Rh(cod)(OH)} ₂]	dppe	6
3	[{Rh(cod)(OH)} ₂]	dppp	16
4	[{Rh(cod)(OH)} ₂]	dppb	13
5	[{Rh(cod)(OH)} ₂]	(<i>R</i>)-binap	66
6	[{Rh(cod)(OH)} ₂]	(<i>R</i>)-segphos (L1)	49
7	[{Rh(cod)(OH)} ₂]	(<i>R</i>)-difluorophos (L2)	0
8	[{Rh(cod)(OH)} ₂]	(<i>R</i>)- L3	63
9	[{Rh(cod)(OH)} ₂]	(<i>R</i>)- L4	0
10	[{Rh(cod)(OH)} ₂]	<i>rac</i> - L5	69
11	[{Rh(C ₂ H ₄) ₂ (OAc)} ₂]	<i>rac</i> - L5	67
12	[{Rh(cod)(OMe)} ₂]	<i>rac</i> - L5	40
13	[{Rh(cod)Cl} ₂]	<i>rac</i> - L5	< 5
14	[Rh(cod) ₂] BF ₄	<i>rac</i> - L5	< 5
15 ^[c]	[{Rh(cod)(OH)} ₂]	<i>rac</i> - L5	59
16 ^[d]	[{Rh(cod)(OH)} ₂]	<i>rac</i> - L5	32

[a] Reaction conditions: **1a** (0.1 mmol), **3a** (0.3 mmol), [Rh^I] (5 mol%), **L** (6 mol%), 0.5 M in toluene, 120°C, 16 h. [b] Yield of isolated product. [c] Octane used as solvent. [d] Dimethylacetamide used as solvent. binap = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl, cod = 1,5-cyclooctadiene, dppb = 1,4-bis(diphenylphosphino)butane, dppe = 1,2-bis(diphenylphosphino)ethane, dppp = 1,3-bis(diphenylphosphanyl)propane.

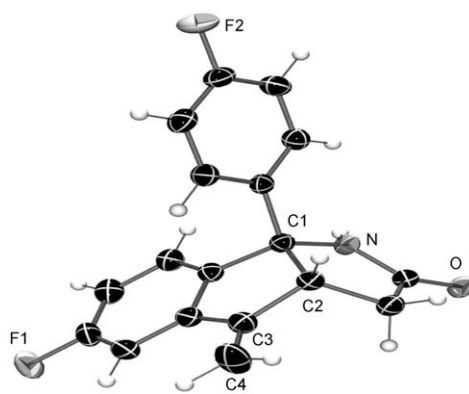
lower conversions (entries 11 and 12). Cationic rhodium(I) and halide ion complexes (entries 13 and 14) are not suitable for the transformation as they cause either allene oligomerization or decomposition of the imine during prolonged reaction times. This reflects the importance of the counterion in the process of generating a competent cyclometalated species **2**.^[13] With any tested catalyst species, we observed only one regio- and diastereoisomer of **6aa**. Besides the metal precursor, the phosphine ligand had a tremendous impact upon the reactivity. Whereas PPh₃ is inactive, bidentate ligands like dppe, dppp, and dppb led to the product **6aa**, although the conversions of the reactions are very low (entries 1–4). Biaryl phosphines display enhanced reactivity, for example, the product yield was 66% with binap (entry 5). A systematic screening led to the conclusion that both the dihedral angle of the biaryl backbone^[14] and the electronic nature of the phosphorous atom have significant influence upon the reactivity of the resulting catalyst. The importance of an electronic tuning of the ligand is most apparent with electron-poor difluorophos (**L2**; 0% yield) compared to the more electron-rich segphos (**L1**; 49% yield). Even more electron-rich phosphine ligands led to enhanced reactivity.^[15] This is especially the case for triMeObiphep (**L3**) and

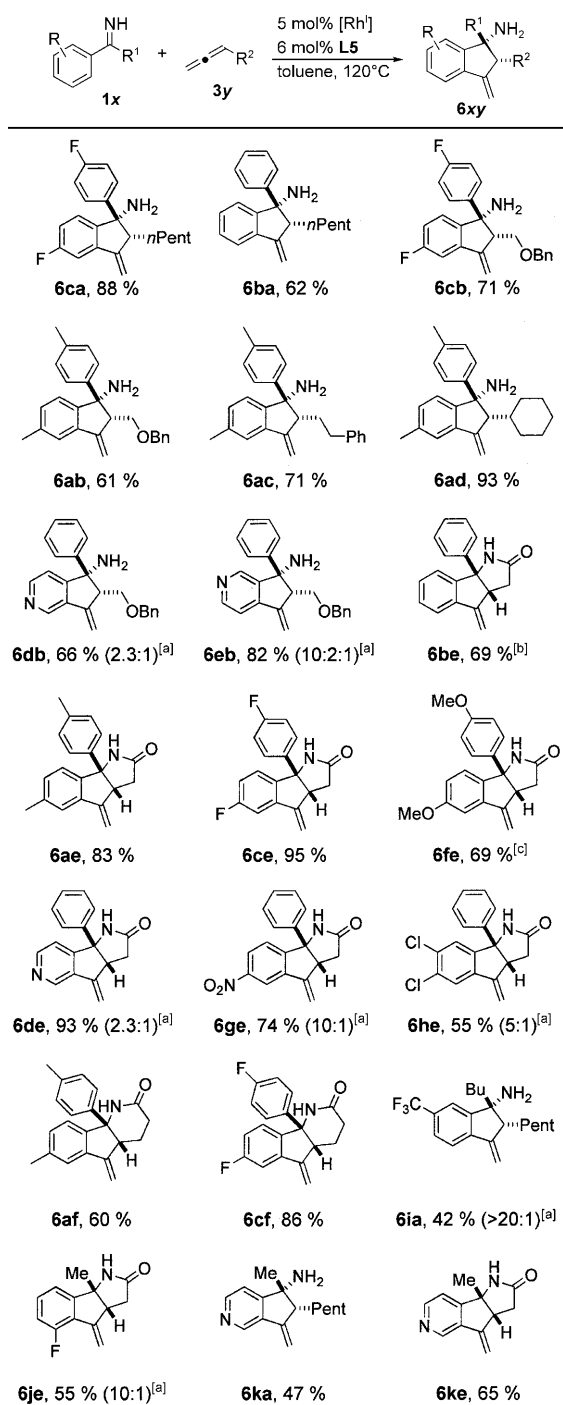
allMeObiphep (**L5**), which give **6aa** in 67% and 69% yields, respectively (entries 8 and 10).^[16] In stark contrast, highly basic phosphine ligands substituted with alkyl groups (**L4**) do not give the product at all (entry 9). The optimal reactivity for the current catalyst system is most conveniently achieved with binap, whereas **L5** is best suited for more reluctant substrate combinations.^[17]

Scheme 2 outlines the scope of the reaction under the aforementioned optimized conditions. Besides symmetrical diaryl ketimines, a variety of electronically different unsymmetrical diaryl ketimines were employed. Substrates bearing less electron-rich aromatic groups are in general more reactive than **1a** (R = R¹ = 4-Me). The observed positional selectivity for the cyclization also indicates the preferential participation of the most electron-poor aromatic group in the cyclometalation step. Positional selectivities between 2.3:1–5:1 were obtained for the 4-pyridyl (**1d**), 3-pyridyl (**1e**), and the 3,4-dichloro (**1h**) phenyl derivatives. The *p*-nitro derivative **6ge** displays a higher selectivity (10:1). Related alkyl aryl ketimines have an attenuated reactivity, but perform well when the aryl group is relatively electron poor [**1i** (R = 3-CF₃, R¹ = Bu), **1j** (R = 3-F, R¹ = Me), **1k** (4-pyridyl, R¹ = Me)]. 3-Fluorophenylimine (**1j**) displays a pronounced *ortho*-fluorine effect giving **6je** in a 10:1 ratio over the product arising from an activation *para* to the fluorine atom.^[18] The allene component **3** can also be varied and several functionalized terminal allenes participate cleanly in the cyclization event. Terminal ester groups [**3e** (R² = CH₂CO₂Et), **3f** (R² = CH₂CH₂CO₂Me)] on the allene allow the capture of the primary amine moiety directly generating the corresponding five- and six-membered lactams.

The relative *syn* configurations of the substituents of the allene and the amine groups of the products **6** were established by nOe spectroscopy as well as by X-ray crystallographic analysis of the lactam derivative **6ce** (Figure 1).^[19]

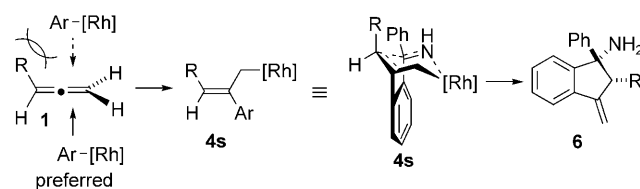
This inherent selectivity of the cyclization event can be rationalized by an initial carborhodation of the allene from the sterically less encumbered face leading to the σ -bound allyl rhodium intermediate **4s** (Scheme 3). Assuming a relatively slow isomerization to other allylic species, **4s** can subsequently undergo the allylation via a closed chair-like transition state, accounting for the observed *syn* stereochemistry of **6**.

**Figure 1.** ORTEP representation of **6ce** (ellipsoids at 50%).

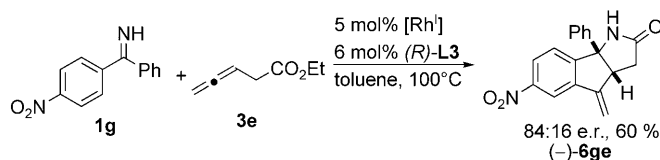


Scheme 2. Scope of the C–H activation/cyclization sequence. Reaction conditions: **1** (0.1 mmol), **3** (3 equiv), [Rh(OH)(cod)]₂ (2.5 mol %), **L5** (6.0 mol %), 0.5 M in toluene, 120 °C, 16 h. [a] Ratio of positional isomers determined by NMR analysis; structure of major product shown. [b] Used 6 mol % **L3**. [c] Chlorobenzene was used instead of toluene. **3e** = Ethyl penta-3,4-dienoate; **3f** = methyl hexa-4,5-dienoate.

Preliminary attempts to develop an enantioselective variant of the C–H activation/cyclization process using **L3** as the prototypical chiral ligand gave rise to (–)-**6ge** in 60 % yield and an enantiomeric ratio of 84:16 (Scheme 4).^[20]



Scheme 3. Rationale for the stereochemical outcome of the reaction.



Scheme 4. Lead result for an enantioselective variant.

In conclusion, we have shown the rhodium(I)-catalyzed C–H functionalizations of unsubstituted ketimines with terminal allenes. Formation of allyl rhodium intermediates enable additions to the directing imine moiety and lead to cyclized products in a highly regio- and diastereoselective manner. As a consequence, this procedure is well suited for a rapid and atom-economical assembly of versatile intermediates from simple starting materials. The observed stereoelectronic effects of the ligand should have broader implications for the design of related processes as well as for the development of catalytic asymmetric processes. Studies in these areas are currently ongoing.

Experimental Section

[Rh(cod)(OH)]₂ (1.14 mg, 2.50 μmol) and **L5** (6.40 mg, 6.00 μmol) were weighed into an oven dried vial equipped with a magnetic stir bar, sealed with a rubber septum, and then flushed with nitrogen. Dry toluene (0.20 mL), ketimine **1a** (20.9 mg, 0.10 mmol), and allene **3a** (33.0 mg, 0.30 mmol) were added to the reaction mixture, which was then degassed by three freeze/pump/thaw cycles and subsequently immersed into a preheated oil bath (120 °C) for 16 h. When TLC analysis indicated the complete conversion, the reaction mixture was cooled to 23 °C, and directly purified on silica gel (10 % EtOAc in pentane, *R_f* = 0.30) yielding 22.0 mg (69 %) of **6aa** as a colorless oil.

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- [1] For representative reviews on C–H bond functionalizations, see: a) G. Dyker, *Angew. Chem.* **1999**, *111*, 1808–1822; *Angew. Chem. Int. Ed.* **1999**, *38*, 1698–1712; b) C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, *34*, 633–639; c) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731–1769; d) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal.* **2003**, *345*, 1077–1101; e) K. Godula, D. Sames, *Science* **2006**, *312*, 67–72; f) F. Kakiuchi, *Top. Organomet. Chem.* **2007**, *24*, 1–33; g) T. Satoh, M. Miura, *Top. Organomet. Chem.* **2007**, *24*, 61–84; h) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173–1193; i) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*,

- 174–238; j) F. Kakiuchi, T. Kochi, *Synthesis* **2008**, 3013–3039; k) J. C. Lewis, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2008**, *41*, 1013–1025; l) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196–5217; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115.
- [2] For reviews on directed C–H bond functionalizations, see: a) F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, *35*, 826–834; b) L. Ackermann, *Top. Organomet. Chem.* **2007**, *24*, 35–60; c) D. Kalyani, M. S. Sanford, *Top. Organomet. Chem.* **2007**, *24*, 85–116; d) C.-H. Jun, E.-A. Jo, J.-W. Park, *Eur. J. Org. Chem.* **2007**, 1869–1881; e) Y. J. Park, J.-W. Park, C.-H. Jun, *Acc. Chem. Res.* **2008**, *41*, 222–234; f) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624–655.
- [3] a) K. Ueura, T. Satoh, M. Miura, *J. Org. Chem.* **2007**, *72*, 5362–5367; b) K. Ueura, T. Satoh, M. Miura, *Org. Lett.* **2007**, *9*, 1407–1409.
- [4] a) S.-G. Lim, J. Hee Lee, C. W. Moon, J.-B. Hong, C.-H. Jun, *Org. Lett.* **2003**, *5*, 2759–2761; b) N. Guimond, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 12050–12051; c) T. Fukutani, N. Umeda, K. Hirano, T. Satoh, M. Miura, *Chem. Commun.* **2009**, 5141–5143.
- [5] a) Y. Kuninobu, A. Kawata, K. Takai, *J. Am. Chem. Soc.* **2005**, *127*, 13498–13499; b) Y. Kuninobu, Y. Tokunaga, A. Kawata, K. Takai, *J. Am. Chem. Soc.* **2006**, *128*, 202–209; c) Y. Kuninobu, Y. Nishina, M. Shouho, K. Takai, *Angew. Chem.* **2006**, *118*, 2832–2834; *Angew. Chem. Int. Ed.* **2006**, *45*, 2766–2768.
- [6] Z.-M. Sun, S.-P. Chen, P. Zhao, *Chem. Eur. J.* **2010**, *16*, 2619–2627.
- [7] a) E. Skucas, J. F. Bower, M. J. Krische, *J. Am. Chem. Soc.* **2007**, *129*, 12678–12679; b) M.-Y. Ngai, E. Skucas, M. J. Krische, *Org. Lett.* **2008**, *10*, 2705–2708; c) S. B. Han, I. S. Kim, H. Han, M. J. Krische, *J. Am. Chem. Soc.* **2009**, *131*, 6916–6917; d) E. Skucas, J. R. Zbieg, M. J. Krische, *J. Am. Chem. Soc.* **2009**, *131*, 5054–5055.
- [8] For a review, see: a) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel, J.-Q. Yu, *Chem. Soc. Rev.* **2009**, *38*, 3242–3272; for contributions from our own laboratory, see: b) T. Seiser, O. A. Roth, N. Cramer, *Angew. Chem.* **2009**, *121*, 6438–6441; *Angew. Chem. Int. Ed.* **2009**, *48*, 6320–6323; c) M. Albicker, N. Cramer, *Angew. Chem.* **2009**, *121*, 9303–9306; *Angew. Chem. Int. Ed.* **2009**, *48*, 9139–9142.
- [9] For some mechanistic and theoretical studies, see: a) Y. Boutadla, D. L. Davies, S. A. Macgregor, A. I. Poblador-Bahamonde, *Dalton Trans.* **2009**, 5820–5831; b) L. Li, W. W. Brennessel, W. D. Jones, *Organometallics* **2009**, *28*, 3492–3500; c) D. L. Strout, S. Zaric, S. Q. Niu and M. B. Hall, *J. Am. Chem. Soc.* **1996**, *118*, 6068–6069; d) M. D. Su, S. Y. Chu, *J. Am. Chem. Soc.* **1997**, *119*, 5373–5383; e) S. Q. Niu, M. B. Hall, *J. Am. Chem. Soc.* **1998**, *120*, 6169–6170; f) A. J. Toner, S. Grundemann, E. Clot, H. H. Limbach, B. Donnadiou, S. Sabo-Etienne, B. Chaudret, *J. Am. Chem. Soc.* **2000**, *122*, 6777–6778.
- [10] a) R. Zimmer, C. U. Dinesh, E. Nandan, F. A. Khan, *Chem. Rev.* **2000**, *100*, 3067–3126; b) S. Ma, *Chem. Rev.* **2005**, *105*, 2829–2872.
- [11] a) P. A. Evans, J. D. Nelson, *J. Am. Chem. Soc.* **1998**, *120*, 5581–5582; b) P. A. Evans, J. D. Nelson, *Tetrahedron Lett.* **1998**, *39*, 1725–1728.
- [12] Unsubstituted ketimines are readily available by the addition of lithium or Grignard reagents to nitriles or from the ketones by a treatment with ammonia and titanium tetrachloride. The purity of the imines **1** is of great importance for the conversion of the reaction. Substituted diaryl ketimines (NBn, NTs, NAc, NCO₂Me) give the corresponding product **6** only very low yields.
- [13] The removal of the aromatic hydrogen atom from the rhodium complex as water, or acetic acid seems to play an important role in the generation of a reactive cyclometalated and/or allylic species.
- [14] S. Jeulin, S. Duprat de Paule, V. Ratovelomanana-Vidal, J.-P. Genet, N. Champion, P. Dellis, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5799–5804.
- [15] The carbonyl stretching frequency of the corresponding [LRh(Cl)CO] complex is a convenient indicator for the relative π acidity of the phosphines ligands: **L1**: $\nu = 2004\text{ cm}^{-1}$, **L2**: $\nu = 2017\text{ cm}^{-1}$, **L4**: $\nu = 1984\text{ cm}^{-1}$, **L5**: $\nu = 2000\text{ cm}^{-1}$, binap: $\nu = 2006\text{ cm}^{-1}$ (data obtained on a Varian 640-IR FT-IR spectrometer).
- [16] The allMeOBiphep ligand (**L5**) was developed at F. Hoffmann-La Roche AG: EP0926151A1. However, its performance in catalytic reactions has never been disclosed. *rac*-**L5** is conveniently prepared in two steps from *tris*-3,4,5-trimethoxyphosphine oxide in 59% yield.
- [17] The obtained e.r. values for **6aa** were: 57:43 ((*R*)-binap), 60:40 (**L1**), 71:29 (**L3**).
- [18] E. Clot, M. Besora, F. Maseras, C. M  gret, O. Eisenstein, B. Oelckers, R. N. Perutz, *Chem. Commun.* **2003**, 490–491.
- [19] Crystallographic data for **6ce**: C₁₈H₁₃F₂NO, M = 297.30, monoclinic, space group C2/c, *a* = 25.9672(6) Å, *b* = 7.3668(2) Å, *c* = 17.6121(5) Å, $\beta = 124.3779(13)^\circ$, *V* = 2780.63(13) Å³, *Z* = 8, *D*_{calc} = 1.420 Mg m^{−3}, *T* = 123 K, reflections collected: 5596, independent reflections: 3183 (*R*_{int} = 0.046), *R*(all) = 0.0660, *wR*(gt) = 0.1334. CCDC 779690 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [20] The absolute configuration of (−)-**6ge** has not yet been determined.