Organic LETTERS

Letter

pubs.acs.org/OrgLett

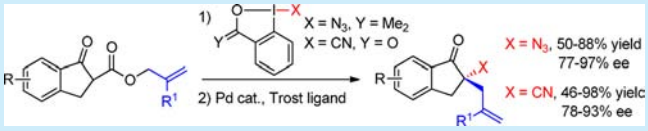
Enantioselective Synthesis of Homoallylic Azides and Nitriles via Palladium-Catalyzed Decarboxylative Allylation

Maria Victoria Vita,[§] Paola Caramenti,[§] and Jerome Waser*[,†]

[†]Laboratory of Catalysis and Organic Synthesis, Ecole Polytechnique Fédérale de Lausanne, EPFL SB ISIC LCSO, BCH 4306, 1015 Lausanne, Switzerland

Supporting Information

ABSTRACT: Azides and nitriles are important building blocks for the synthesis of nitrogen-containing bioactive compounds. The first example of enantioselective palladium-catalyzed decarboxylative allylation of α-azido and cyano β-ketoesters is reported. Indanone derivatives were obtained in 50−88% yield/77−97% ee and 46−98% yield/78−93% ee for azide and nitrile substituents, respectively. The required starting materials were synthesized in one step from ketoesters via electrophilic azidation and cyanation using benziodoxole hypervalent iodine reagents. The products could be easily converted into useful nitrogen-containing building blocks, such as triazoles, amides, or α- and β- amino ketones.



Nitrogen-containing functional groups are omnipresent in synthetic and natural bioactive compounds. Among them, azides[1] and nitriles[2] occupy a privileged position. They are highly useful as nonbasic precursors of amines. In addition, they can be transformed in a multitude of other functional groups and can be used in cycloaddition reactions to give a broad range of heterocycles (Figure 1). New methods giving

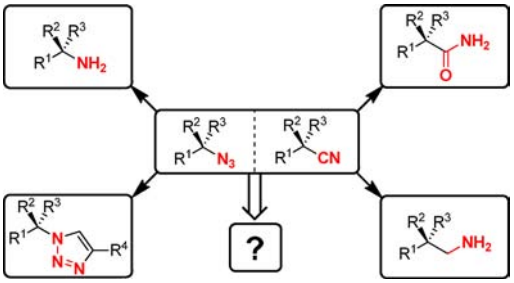


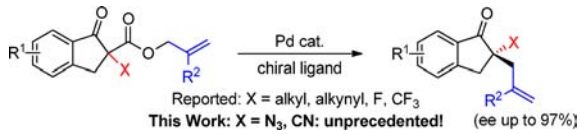
Figure 1. Enantiopure tertiary azides and cyanides: versatile building blocks, but challenging to access.

access to nitriles and azides, especially in enantiopure form, are therefore highly useful for both synthetic and medicinal chemistry. Whereas numerous methods are available for the enantioselective synthesis of secondary azides and nitriles, accessing tertiary derivatives is more challenging.

Among the methods used for the enantioselective synthesis of highly substituted stereocenters, the Tsuji−Trost palladium-catalyzed decarboxylative allylation has been especially successful.[3] Nevertheless, to the best of our knowledge, this methodology has never been used for the synthesis of homoallylic azides, and there are only racemic examples for cyanides.[3c,4] This is an important limitation when considering the versatility of these building blocks. In general, the Tsuji−Trost decarboxylation has been only rarely used to synthesize homo- and bis-homo allylic amines.[5] In 2015, Stoltz and co-workers, developed in particular an elegant Mannich addition/asymmetric decarboxylative allylation sequence to access bis-homo allylic amines.[5d]

Indan(on)es are privileged structures in bioactive compounds, and nitrogen-substituted derivatives are especially important.[6] Nevertheless, the enantioselective synthesis of α-azido and cyano indanones has been limited to the azidation of ketoester derivatives[7] and the conjugate addition or Mannich reaction of α-cyano indanones.[8] The Tsuji−Trost decarboxylation, although highly successful in the case of other type of substituents,[3f,9] has never been reported in the case of cyanides and azides (Scheme 1). Herein, we would like to report the first

Scheme 1. Enantioselective Synthesis of Indanones via the Tsuji−Trost Decarboxylative Allylation



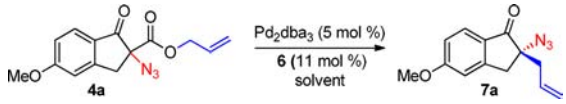
example of highly enantioselective palladium-catalyzed decarboxylative allylation proceeding on cyano- and azido-substituted indanone derivatives. The required substrates were easily synthesized by the azidation or cyanation of ketoesters using hypervalent iodine reagents.

We started our investigations with the synthesis of the required azido- and cyano-allyl ketoesters **4** and **5**. The desired indanones could be accessed in good yield by the reaction with hypervalent iodine reagents **2** or **3** without any other additives using methods developed in our group[10] and by Chen and co-

Received: October 16, 2015
Published: November 18, 2015

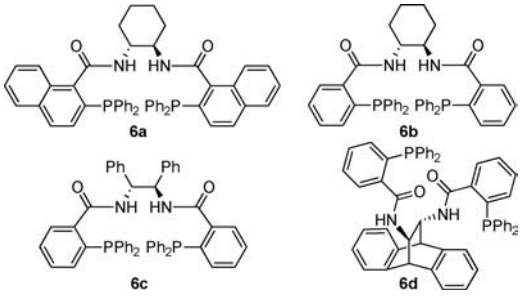
DOI: 10.1021/acs.orglett.5b03002
Org. Lett. 2015, 17, 5832−5835

Table 1. Optimization of the Decarboxylative Allylation of Azide 4a



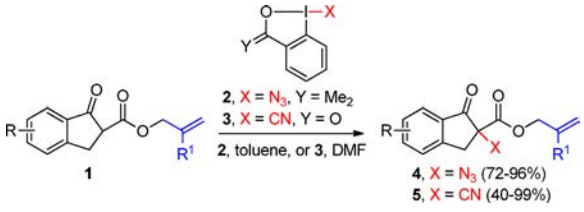
entry	ligand	solvent	yield (%)[a]	ee (%)[b]
1	**6a**	MTBE	31	71
2	**6a**	toluene	38	70
3	**6a**	CH_3CN	50	68
4	**6a**	CH_2Cl_2	93	60
5	**6a**	Et_2O	27	71
6	**6a**	dioxane	38	42
7	**6a**	THF	88	79
8	**6b**	THF	10	30
9	**6c**	THF	< 5	nd
10	**6d**	THF	15	49
11	**6a**	THF	88	86[c]

[a]Reaction conditions: Substrate **4a** (0.012 mmol), $Pd_2(dba)_3$ (5 mol %), **6** (11 mol %) and solvent (0.2 M) at 25 °C. The NMR yield is measured in comparison with the internal standard 1,3,5-trimethoxybenzene. [b]Obtained by chiral HPLC. [c]At 0.4 M at −20 °C for 12 h.



workers (Scheme 2).[11] Unfortunately, the method could not be used to access the corresponding tetralones, due to competitive elimination and aromatization to naphthol derivatives.

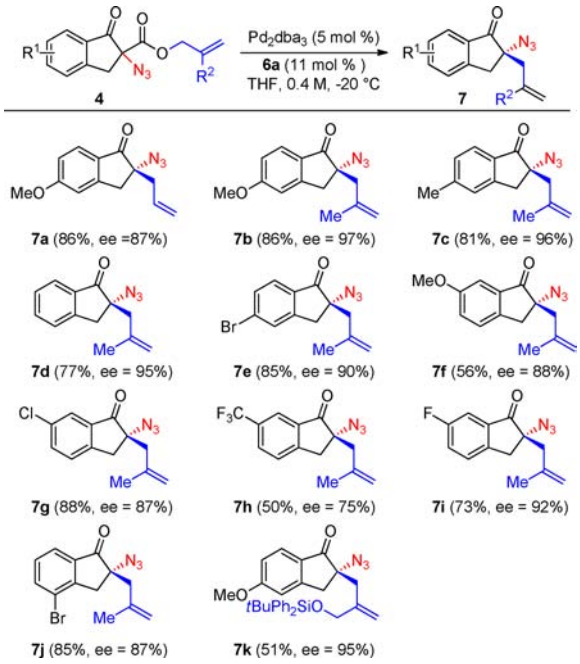
Scheme 2. Synthesis of α-Azido and Cyano Allyl Ketoesters 4 and 5



We then turned to the optimization of the decarboxylative allylation for azide **4a** (Table 1).[12] When using Pd(Cp)-Cinnamyl as catalyst precursor as in our previous work on the decarboxylative allylation of alkynyl-substituted ketoesters,[9h] only low conversion was observed. Better results were obtained using $Pd_2(dba)_3$ with Trost's bisphosphine ligand **6a**, and the desired product **7a** was obtained in 31% yield and 71% ee, but 5 mol % catalyst were needed to reach full conversion (Table 1, entry 1).[12] A strong dependence of both yield and enantioselectivity on solvent became apparent (Table 1, entries 2−7). Whereas moderate yields and ee were observed in toluene and acetonitrile (Table 1, entries 2 and 3), 93% yield of **7a** was obtained in dichloromethane, albeit at the cost of ee (Table 1, entry 4). From the tested ether solvents, THF gave the best result, with 88% yield and 79% ee (Table 1, entry 7). Other Trost bisphosphine ligands gave inferior results (Table 1, entries 8−10).[13] Finally, the enantioselectivity could be improved to 86% by working in more concentrated solution at −20 °C (Table 1, entry 11).

The scope of the decarboxylative allylation of azides was then examined (Scheme 3). The use of methallyl substrate **4b** gave

Scheme 3. Scope of the Decarboxylative Allylation with Azides 4[a]



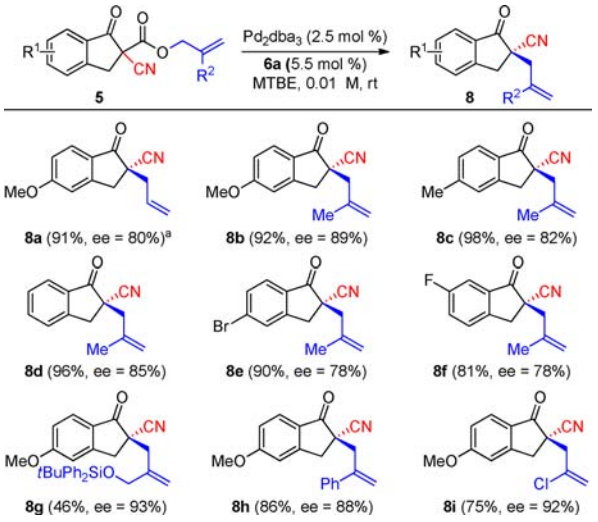
[a]Reaction conditions: Substrate **4** (0.20 mmol), $Pd_2(dba)_3$ (5 mol %), **6a** (11 mol %) and THF (0.4 M) at −20 °C, 10−15 h. The isolated yields after column chromatography are given; ee values are obtained by chiral HPLC.

the desired product **7b** in improved 97% ee. Product **7c** and **7d** bearing either a methyl group or no substituent in C5 position also gave the products in good yield and enantioselectivity. Interestingly, a 5-bromo group was also tolerated, despite the fact that a palladium(0) catalyst is used (product **7e**). Substitution at the C6 position was also possible, although in some cases lower yields and ee values were obtained (products **7f−i**). The decarboxylative allylation was also successful with a 4-bromo substituent (product **7j**). Finally, the use of a more functionalized allyl group bearing a protected alcohol was also possible, as demonstrated by the formation of product **7k** in 51% yield and 95% ee.[14]

In the case of cyano substrate **5a**, the conditions used in our previous work for the decarboxylative allylation of α-alkynyl allyl ketoesters (2 mol % Pd(Cp)Cinnamyl, 2.5 mol % **6a**, MTBE, 0.1 M, rt) did not need to be changed extensively.[9h,12] In fact, working in more diluted conditions (0.01 M) and with higher catalyst/ligand loading (5 and 5.5 mol %, respectively) was enough to give the desired allyl cyanides **8a** in 91% yield and 80% ee (Scheme 4). For methallyl-based substrates, however, better results were obtained with Pd_2dba_3 as catalyst precursor (92% yield and 89% ee for **8b**). Irrespectively of the substitution pattern or electronic properties of the substituents on the benzene ring, the desired methallyl cyanides **8b−f** were obtained in very good yields (81−98%), but the ee values were

DOI: 10.1021/acs.orglett.5b03002
Org. Lett. 2015, 17, 5832−5835

Scheme 4. Scope of the Decarboxylative Allylation with Nitriles 5[b]

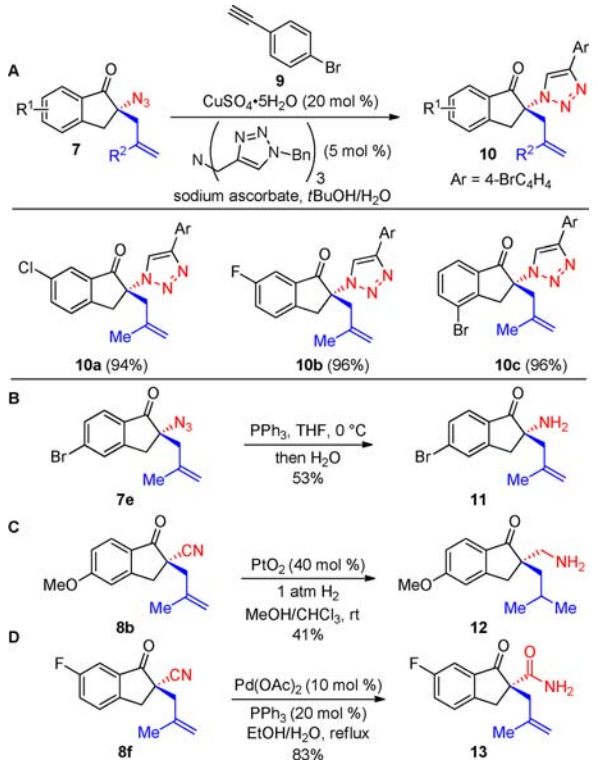


[a]Using 5 mol % PdCpCinnamyl as catalyst precursor. [b]Reaction conditions: Substrate **5** (0.20 mmol), $Pd_2(dba)_3$ (2.5 mol %), **6a** (5.5 mol %), and THF (0.01 M) at 25 °C, 6–48 h. The isolated yields after column chromatography are given; ee values are obtained by chiral HPLC.

lower than for azides (78–89%). Modification of the substituent on the alkene was also possible as a protected alcohol, an aryl, or a chloride group (products **8g–i**). Protected alcohol **8g** was obtained in 93% ee, which is the highest enantioselectivity observed for this class of substrates.

The obtained products could be easily transformed into useful nitrogen-containing building blocks (Scheme 5).[7b,15]

Scheme 5. Modifications of the Obtained Products



Copper-catalyzed [3 + 2]-cycloaddition of azides **7** with aromatic alkyne **9** gave triazoles **10a–c** in 94–96% yield (Scheme 5, **A**).[7b] Staudinger reduction of azide **7e** led to α-amino ketone **11**,[15a] whereas hydrogenation of nitrile **8b** gave β-amino ketone **12** (Scheme 5, **B** and **C**).[15b] Finally, amide **13** was obtained in 83% yield by hydration of nitrile **8f** in the presence of a palladium catalyst (Scheme 5, **D**).[15c]

In conclusion, we have reported the first example of enantioselective palladium-catalyzed decarboxylative allylation proceeding next to cyano and azido groups. The reaction proceeded with indanone derivatives in 50–88% yield/77–97% ee and 46–98% yield/78–93% ee with azide and nitrile substituents, respectively. A broad range of functional groups was tolerated on the benzene ring and the alkene. The required indanone starting materials were obtained by the reaction of benziodoxole hypervalent iodine reagents with ketoesters. The obtained products were easily transformed into useful nitrogen-containing building blocks, such as triazoles, amides, and amines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03002.

Chemical data for C15 H15 N O (CIF)

Experimental procedures and analytical data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jerome.waser@epfl.ch

Author Contributions

[§]M.V.V. and P.C. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank EPFL and the Swiss National Science Foundation (SNSF, Grant No. 200020_134550) for financial support. We thank Dr. Kurt Schenk from the Institute of the Physics of Biological Systems at EPFL for performing the X-ray analysis on compound **8c**.

■ REFERENCES

(1) (a) Brase, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188. (b) Lutz, J.-F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1018. (c) Meldal, M.; Tornoe, C. W. *Chem. Rev.* **2008**, *108*, 2952. (d) *Organic Azides: Syntheses and Applications*; Bräse, S., Banert, K. Eds.; Wiley: 2009.

(2) (a) Fatiadi, A. J. *Preparation and Synthetic Applications of Cyano Compounds*; Wiley: New York, 1983. (b) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. *J. Med. Chem.* **2010**, *53*, 7902. (c) Wang, T.; Jiao, N. *Acc. Chem. Res.* **2014**, *47*, 1137.

(3) (a) Shimizu, I.; Yamada, T.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3199. (b) Shimizu, I.; Tsuji, J. *J. Am. Chem. Soc.* **1982**, *104*, 5844. (c) Tsuda, T.; Chujo, Y.; Nishi, S.; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381. (d) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044. (e) Liu, Y.; Han, S.-J.; Liu, W.-B.; Stoltz, B. M. *Acc. Chem. Res.* **2015**, *48*, 740. (f) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846.

DOI: 10.1021/acs.orglett.5b03002
Org. Lett. 2015, 17, 5832–5835

(4) (a) Tsuji, J.; Yamada, T.; Minami, I.; Yuhara, M.; Nisar, M.; Shimizu, I. *J. Org. Chem.* **1987**, *52*, 2988. (b) Waetzig, S. R.; Rayabarapu, D. K.; Weaver, J. D.; Tunge, J. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4977. (c) Recio, A.; Tunge, J. A. *Org. Lett.* **2009**, *11*, 5630.
(5) (a) Burger, E. C.; Tunge, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 10002. (b) Lang, S. B.; O'Nele, K. M.; Tunge, J. A. *J. Am. Chem. Soc.* **2014**, *136*, 13606. (c) Korch, K. M.; Eidamshaus, C.; Behenna, D. C.; Nam, S.; Horne, D.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2015**, *54*, 179. (d) Numajiri, Y.; Pritchett, B. P.; Chiyoda, K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2015**, *137*, 1040.
(6) (a) McLean, S.; Lin, M.-S.; Macdonald, A. C.; Trotter, J. *Tetrahedron Lett.* **1966**, *7*, 185. (b) Virtanen, R.; Savola, J. M.; Saano, V. *Arch. Int. Pharmacodyn. Ther.* **1989**, *297*, 190. (c) Savola, J. M.; Hill, M.; Engstrom, M.; Merivuori, H.; Wurster, S.; McGuire, S. G.; Fox, S. H.; Crossman, A. R.; Brotchie, J. M. *Mov. Disord.* **2003**, *18*, 872. (d) Bell, I. M.; Gallicchio, S. N.; Wood, M. R.; Quigley, A. G.; Stump, C. A.; Zartman, C. B.; Fay, J. F.; Li, C.-C.; Lynch, J. J.; Moore, E. L.; Mosser, S. D.; Prueksaritanont, T.; Regan, C. P.; Roller, S.; Salvatore, C. A.; Kane, S. A.; Vacca, J. P.; Selnick, H. G. *ACS Med. Chem. Lett.* **2010**, *1*, 24.
(7) (a) Shibatomi, K.; Soga, Y.; Narayama, A.; Fujisawa, I.; Iwasa, S. *J. Am. Chem. Soc.* **2012**, *134*, 9836. (b) Deng, Q.-H.; Bleith, T.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc.* **2013**, *135*, 5356.
(8) (a) Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928. (b) Wang, B.; Wu, F.; Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 768. (c) Li, H.; Song, J.; Deng, L. *Tetrahedron* **2009**, *65*, 3139. (d) Lee, J. H.; Kim, D. Y. *Adv. Synth. Catal.* **2009**, *351*, 1779. (e) Lee, H. J.; Woo, S. B.; Kim, D. Y. *Tetrahedron Lett.* **2012**, *53*, 3374.
(9) (a) Nakamura, M.; Hajra, L.; Endo, K.; Nakamura, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 7248. (b) Burger, E. C.; Barron, B. R.; Tunge, J. A. *Synlett* **2006**, *2006*, 2824. (c) Belanger, E.; Houze, C.; Guimond, N.; Cantin, K.; Paquin, J.-F. *Chem. Commun.* **2008**, 3251. (d) Bélanger, É.; Pouliot, M.-F.; Courtemanche, M.-A.; Paquin, J.-F. *J. Org. Chem.* **2012**, *77*, 317. (e) Trost, B. M.; Schaffner, B.; Osipov, M.; Wilton, D. A. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 3548. (f) Shibata, N.; Suzuki, S.; Furukawa, T.; Kawai, H.; Tokunaga, E.; Yuan, Z.; Cahard, D. *Adv. Synth. Catal.* **2011**, *353*, 2037. (g) Behenna, D. C.; Mohr, J. T.; Sherden, N. H.; Marinescu, S. C.; Harned, A. M.; Tani, K.; Seto, M.; Ma, S.; Novák, Z.; Krout, M. R.; McFadden, R. M.; Roizen, J. L.; Enquist, J. A.; White, D. E.; Levine, S. R.; Petrova, K. V.; Iwashita, A.; Virgil, S. C.; Stoltz, B. M. *Chem. - Eur. J.* **2011**, *17*, 14199. (h) Vita, M. V.; Mieville, P.; Waser, J. *Org. Lett.* **2014**, *16*, 5768.
(10) (a) Vita, M. V.; Waser, J. *Org. Lett.* **2013**, *15*, 3246. First synthesis of reagent **2**: (b) Zhdankin, V. V.; Kuehl, C. J.; Krasutsky, A. P.; Formaneck, M. S.; Bolz, J. T. *Tetrahedron Lett.* **1994**, *35*, 9677. (c) Zhdankin, V. V.; Krasutsky, A. P.; Kuehl, C. J.; Simonsen, A. J.; Woodward, J. K.; Mismash, B.; Bolz, J. T. *J. Am. Chem. Soc.* **1996**, *118*, 5192.
(11) (a) Wang, Y.-F.; Qiu, J.; Kong, D.; Gao, Y.; Lu, F.; Karmaker, P. G.; Chen, F.-X. *Org. Biomol. Chem.* **2015**, *13*, 365. First synthesis of reagent **3**: (b) Zhdankin, V. V.; Kuehl, C. J.; Krasutsky, A. P.; Bolz, J. T.; Mismash, B.; Woodward, J. K.; Simonsen, A. J. *Tetrahedron Lett.* **1995**, *36*, 7975.
(12) See Supporting Information for a full list of tested conditions for substrates **4a,b** and **5a,b**. A single crystal was grown by slow diffusion of the solution of **8c** in EtOAc/heptane mixture to determine its absolute configuration. Supplementary crystallographic data for this compound have been deposited at the Cambridge Crystallographic Data Centre (CCDC 1418044) and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif. The absolute configuration of the other substrates was assigned by analogy.
(13) When ^{t}Bu-PHOX (Pfaltz-Helmchen-Williams ligand) was used as ligand in the reaction, no product was obtained in the case of azide-substituted ketoesters. For cyano-substituted ketoesters, the product was obtained in 94% yield, but in racemic form.
(14) Preliminary experiments with linear ketoesters gave less than 10% conversion. Further investigations will be needed for this challenging class of substrates.
(15) (a) Rossi Paccani, R.; Donati, D.; Fusi, S.; Latterini, L.; Farina, G.; Zanirato, V.; Olivucci, M. *J. Org. Chem.* **2012**, *77*, 1738. (b) Cusack, K.; Scott, B.; Arnold. L.; Ericsson, A. BASF U.S. Patent 2003/153568 A1, August 14, 2003. (c) Kim, E. S.; Kim, H. S.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 2973.

DOI: 10.1021/acs.orglett.5b03002
Org. Lett. 2015, 17, 5832−5835