JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Enantioselective Alkyne Conjugate Addition Enabled by Readily Tuned Atropisomeric *P,N*-Ligands

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Supporting Information

ABSTRACT: By the nature of its structure, the 5-membered chiral biaryl heterocyclic scaffold represents a departure from 6-membered *P,N*-ligands that facilitates tuning and enables ligand evolution to address issues of selectivity and reactivity. In this vein, the Cu-catalyzed enantioselective conjugate alkynylation of Meldrum's acid acceptors is reported using Me-StackPhos. Enabled by this new ligand, the reaction tolerates a wide range of alkynes furnishing the products in high yields and excellent enantioselectivity. The transformation provides access to highly useful chiral β-alkynyl Meldrum's acid building blocks as demonstrated by an efficient enantioselective synthesis of the preclinical agent OPC 51803.

Enantioselective catalysis is an important endeavor, broadly adopted in academic and industrial laboratories for the assembly of chiral compounds.[1] The success of these reactions depends on effective transfer of the chiral information from the catalyst to the substrates and, for organometallic reactions, it is very difficult to identify chiral ligands that satisfactorily perform over a broad range of transformations. Ligands that meet this criterion have been dubbed privileged, and families of these ligands have often been prepared to meet the selectivity demands for individual reactions.[2] One example of this is BINAP, whose C_2-symmetric chiral biaryl structure is based on binaphthalene (Figure 1).[3] The fused benzenoid aromatic architecture facilitates

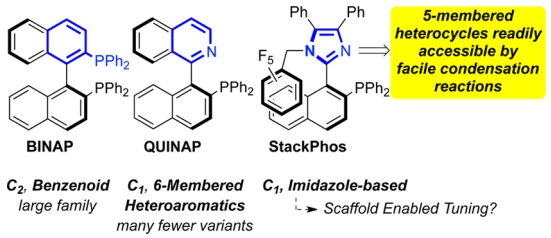


Figure 1. Atropisomeric bisphosphine and *P,N*-ligands.

the preparation of diverse analogues and indeed many different chiral biaryl ligands based on this scaffold have been prepared and demonstrated to catalyze transformations with high levels of enantioselectivity.[4]

Inclusion of a nitrogen heterocycle in place of one of the diphenylphosphino naphthalenes results in a C_1 symmetric chiral biaryl *P,N*-ligand, the parent of which is QUINAP[5] (Figure 1). Complexes of these ligands exhibit unique dihedral and bite angles, and impart both steric and electronic differentiation, resulting in exceptional selectivity in different transformations based on a variety of different metal centers.[6] For ligand tuning, the parent 6-membered heterocycle has been varied resulting in Quinazolinap,[7] Pyphos,[8] and PINAP,[9] and analogues thereof respectively; but despite their unique properties and potential, the family of ligands that has been built up around the QUINAP framework is relatively small in comparison. Although many basic heterocycles could potentially be incorporated, these *P,N*-ligands are comprised of σ-bond linked 6-membered heteroarenes which, in general, offer less modular syntheses than 5-membered ring nitrogen heterocycles, perhaps limiting the fine-tuning process. We recently reported StackPhos,[10] an imidazole-based axially chiral *P,N*-ligand. Because 5-membered ring heterocycles are prepared by simple condensation reactions, we envisioned that the distinctive nature of this ligand scaffold could enable fine-tuning and therefore offer the opportunity to rapidly address selectivity/reactivity problems encountered with *P,N*-ligands (Figure 1). Herein we report the rapid identification of a highly active catalyst system for the enantioselective preparation of β-alkynyl Meldrum's acids.

Enantioselective conjugate addition reactions are important transformations for the assembly of β-chiral carbonyl compounds.[11] Within this reaction class, unsaturated Meldrum's acids are excellent electrophiles and the ensuing adducts are highly versatile synthetic intermediates.[12] In a series of elegant papers, Carreira reported the direct catalytic enantioselective conjugate addition of *in situ* generated Cu-acetylides to Meldrum's acids.[13] After extensive screening (~25 diverse ligands from different classes), the authors developed PINAP; however, this ligand was optimal only for addition of phenylacetylenes to γ-branched alkylidene acceptors. Fillion later developed a Rh-catalyzed addition to benzylidene acceptors using a bisphosphine ligand, but 15 mol % of catalyst was required and the scope was limited to using trimethylsilylacetylene as the nucleophile.[14] As intimated in these and other reports,[13−16] there are few asymmetric methods to access these useful compounds, particularly with benzylidene acceptors and nonaryl alkynes, necessitating new catalyst systems.[17]

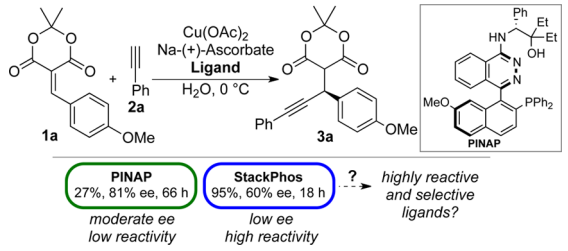
StackPhos has proven to be a highly versatile ligand for alkynylation reactions, demonstrating high enantioselectivity and reactivity in addition to iminium ions and acyl quinolinium salts;[10,18,19] but, to-date, no other types of reactions have been reported. The 5-membered heterocyclic framework embedded in the ligand might provide a platform for evolving new ligands to meet unmet needs and this reaction was chosen for initial studies

Received: January 11, 2017
Published: February 16, 2017

DOI: 10.1021/jacs.7b00363
J. Am. Chem. Soc. 2017, 139, 3352−3355

to this end. Preliminary work employed StackPhos for the addition of phenylacetylene **2a** to Meldrum's acid **1a** using $Cu(OAc)_2$ and sodium ascorbate to reduce Cu(II) to Cu(I). In the event, adduct **3a** was isolated in 95% yield and 60% ee after 18 h (Scheme 1). In comparison, PINAP afforded **3a** in 27% yield

Scheme 1. Direct Alkyne Conjugate Addition to Meldrum's Acids

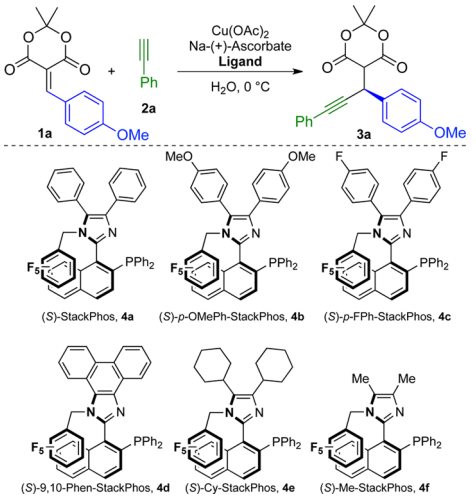


and 81% ee after 66 h.[15] Although the selectivity decreased with StackPhos, the reactivity was greatly enhanced. Encouraged by these results and the ligand tuning potential, we directed our efforts toward the development of asymmetric conjugate alkynylation reactions with the goal of developing a ligand that could impact both selectivity and reactivity.

At the outset, it was unclear what the effects of ligand modification might be. Phosphine substitution can in principle be achieved with all *P*,*N*-ligands,[20] but changing the substitution on the imidazole would uniquely affect steric and electronic properties and, as such, these changes were explored. New chiral ligands were straightforward to prepare via condensation with 2-hydroxynaphthaldehyde and various diketones;[21] and, for comparison, the candidates were screened in the previous reaction (Table 1).[15] Substitution of the phenyl groups with electron donating (-OMe, **4b**) and electron withdrawing groups (-F, **4c**) in the *para*-position yielded ligands that provided adduct **3a** with increased selectivity (entries 2,3). Interestingly, the ee improved to ~75% regardless of donating or withdrawing nature, but the reactivity was greatly reduced with *p*-F-Ph-StackPhos **4c**. Locking the phenyl groups in a planar orientation with the phenanthroquinone derived ligand **4d** yielded **3a** in 75% with 65% ee (entry 4). A common strategy to increase enantioselectivity is to increase the steric demand of the ligand; however, using the cyclohexyl ligand **4e**, the reactivity was restored to the level observed with the parent ligand (entry 1 vs 5), but the ee remained at 60%. Finally, using the less sterically demanding Me-StackPhos **4f**, adduct **3a** was isolated in 81% with 92% ee. This result was unexpected, but satisfactory levels of both selectivity and reactivity were realized and the scope of the reaction was next explored. Configurational stability studies on **4f** revealed that the barrier to rotation of the free Me-StackPhos ligand at 75 °C in DCE is 27.4 kcal/mol,[21] which is very similar to values observed for PINAP ligands,[13] and high enough to be of practical significance for catalysis.

As mentioned above, we were particularly interested in exploring benzylidene acceptors and nonaryl alkyne nucleophiles. Using ligand **4f**, the alkyne scope was first examined. As can be seen in Table 2, phenylacetylenes function well in the reaction to provide the products in excellent ee (91%, **3b**/**c**), but they are sensitive to sterics with the 2,6-dimethyl adduct **3d** being formed in 76% ee. Particular emphasis was placed on non-aromatic alkynes, and it can be seen that excellent ee's can be attained with a broad range of nucleophiles including protected propargyl alcohols (**3f**/**g**) and amines (**3h**/**i**), TMS-acetylene

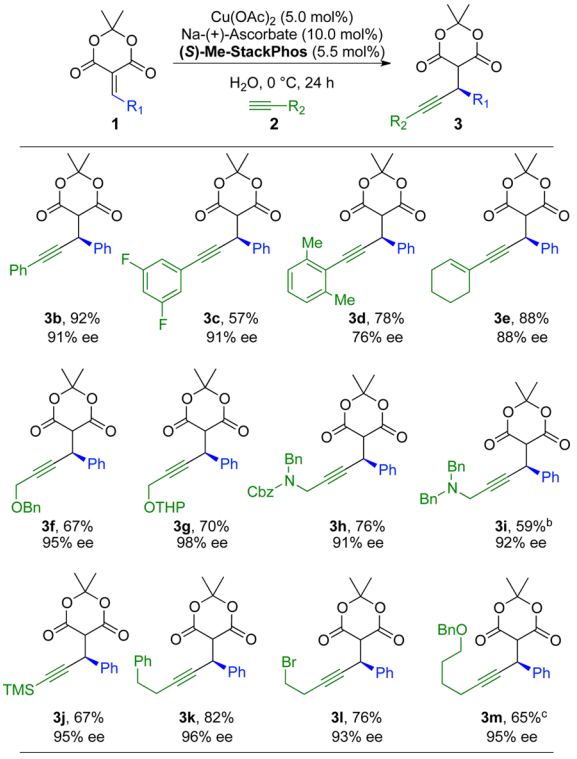
Table 1. Ligand Optimization[a]



entry	ligand	yield (%)[b]	ee (%)[c]
1	(S)-StackPhos, **4a**	95	60
2	(S)-*p*-OMePh-StackPhos, **4b**	84	75
3	(S)-*p*-FPh-StackPhos, **4c**	40	76
4	(S)-9,10-Phen-StackPhos, **4d**	75	65
5	(S)-Cy-StackPhos, **4e**	95	60
6	(S)-Me-StackPhos, **4f**	81	92

[a]Conditions: $Cu(OAc)_2$ (5 mol %), Na(+)-ascorbate (10 mol %), ligand (5 mol %), alkyne (5 equiv), 18 h. [b]Isolated yield. [c]ee determined after conversion to amide using chiral HPLC; see SI for full details.

Table 2. Alkyne Substrate Scope Studies[a]



[a]Conditions: $Cu(OAc)_2$ (5 mol %), Na(+)-ascorbate (10 mol %), (S)-Me-StackPhos (5 mol %), alkyne (5 equiv), H_2O, 24 h; isolated yields; ee determined after conversion to amide using chiral HPLC. [b]Solvent = H_2O:toluene (1:1) with 1.2 equiv. alkyne. [c]Reaction time = 48 h.

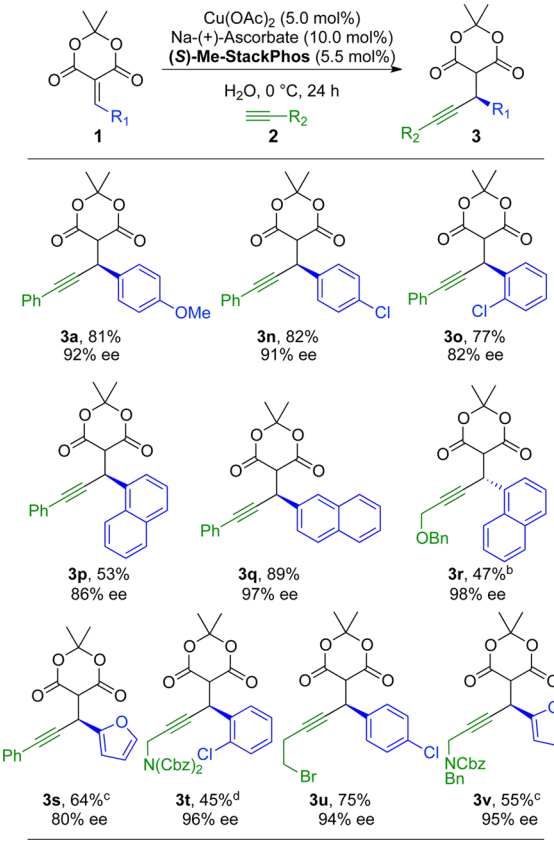
DOI: 10.1021/jacs.7b00363
J. Am. Chem. Soc. 2017, 139, 3352–3355

(**3j**) and even alkyl alkynes (**3k**/**m**). Such broad tolerance to produce the products in >90% ee is fairly uncommon in catalytic enantioselective alkyne addition reactions.

It should also be noted that the reaction medium is water. Although this could be considered green and offer the potential advantages of homogeneous biphasic liquid−liquid systems,[22] in some instances this presents practical challenges, particularly with insoluble solid reagents. Although most alkynes explored here did not present a problem, it was found that toluene could be used as a cosolvent (1:1, H_2O:toluene). Using the mixed solvent system in the reaction forming **3i** (and also below), this solubility issue could be overcome to achieve acceptable levels of reactivity and high enantioselectivity thereby removing any limitations imposed by substrate properties. Furthermore, with increased solubility/miscibility, the amount of alkyne could be reduced to 1.2 mol equiv.

With these successes, we shifted our attention to benzylidene acceptors, first with phenylacetylene and then alternative alkynes (Table 3). Using methyl ligand **4f** with **2a** as the nucleophile, *β*-aryl Meldrum's acids were obtained in high enantiomeric excess. *β*-Alkyl Meldrum's acids provided the products in low optical purity.[21] Several additional alkynes were also employed here and the selectivities were generally higher than with phenylacetylene. Interestingly, although phenylacetylene was used to screen conditions and is frequently used as a prototypical alkyne in many types of systems, these results indicate that it is not necessarily the best alkyne as it was outperformed by the more functionalized nucleophiles examined in this study. This was reassuring as the adducts of more functionalized alkynes in both Tables 2 and 3 would be highly useful in synthetic schemes *vide infra*.

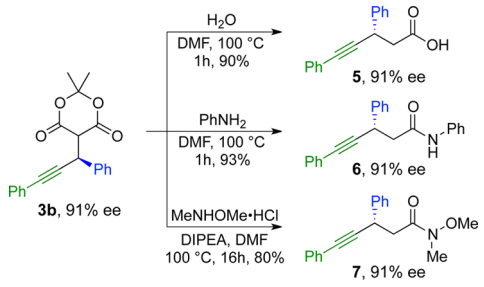
Table 3. Substrate Scope[a]



[a]Conditions: $Cu(OAc)_2$ (5 mol %), Na(+)-ascorbate (10 mol %), (*S*)-Me-StackPhos (5 mol %), alkyne (5 equiv), H_2O, 24 h; isolated yield; ee determined after conversion to amide using chiral HPLC. [b]With (*R*)-Me-StackPhos at rt. [c]Reaction time = 36h. [d]Solvent = H_2O:toluene (1:1) with 1.2 equiv. alkyne.

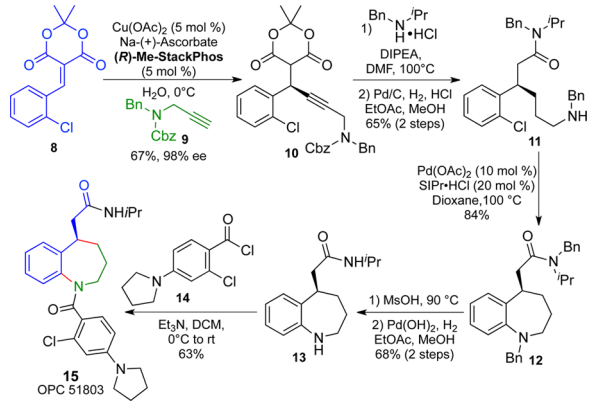
To probe the utility of these interesting building blocks, single step transformations of chiral *β*-alkynyl Meldrum's acid derivatives were performed to access diverse *β*-alkynyl carbonyl compounds **5**−**7** (Scheme 2). Chiral *β*-alkynyl acids are pharmaceutically relevant compounds with diverse biological activities. Even very simple compounds have been identified as PDE IV inhibitors, TNF inhibitors, GPR40 receptor agonists, and GRP receptor antagonists,[23] but these compounds are generally obtained as single enantiomers by classical resolution and would benefit from an enantioselective synthesis. Without the loss of ee, the Meldrum's acid **3b** was smoothly converted to the acid **5**, secondary amide **6**, and the Weinreb amide **7**, which provides a convenient handle for further transformations.[21,24]

Scheme 2. Transformations *β*-Alkynyl Meldrum's Acids



We were particularly interested in this enantioselective transformation because the products should be highly useful synthons toward biologically active compounds. To this end, we began to look at compounds such as OPC 51803 **15** (Scheme 3), currently accessed as a single enantiomer after separating diastereomers prepared by esterification of the racemic core with a nonracemic alcohol and then conversion to the *iso*-propyl amide.[25a] Using enantioselective conjugate addition enabled by Me-StackPhos, the synthesis of **15**, a preclinical agent under study for metabolic disorders and also the first nonpeptide agonist for human AVP V2-receptors, was readily achieved.[25] Under the standard reaction conditions, but with the enantiomeric ligand (*R*)-Me-StackPhos, addition of propargyl amine **9** to Meldrum's acid acceptor **8** gave adduct **10** in 67% yield with 98% ee (Scheme 3). Amide formation with benzyl protected *iso*-propylamine

Scheme 3. Synthesis of OPC 51803



DOI: 10.1021/jacs.7b00363
J. Am. Chem. Soc. 2017, 139, 3352−3355

hydrochloride followed by hydrogenation then provided **11** in 65% yield over 2 steps. Pd-catalyzed intramolecular C−N bond formation required the use of the crucial SIPr NHC ligand[26] to afford **12** in 84% yield. Benzyl deprotection furnished **13** in 68% yield over 2 steps. Finally, amide bond formation with acid chloride **14** and amine **13** afforded **15**, OPC 51803, in 63 % yield.[21]

In summary, we have demonstrated that, by the nature of its structure, the 5-membered biaryl heterocyclic scaffold facilitates tuning and enables ligand evolution to address issues of selectivity and reactivity. As shown here, this complementary ligand set represents a departure from the 6-membered biaryl scaffold and should enable new transformations with C_1-symmetric *P,N*-ligands. Studies to this end are currently underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b00363.

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

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Science Foundation (CHE-1362498) and the University of Florida for their generous support of our programs. We thank Dr. Flavio S. P. Cardoso for preliminary experiments.

■ REFERENCES

(1) (a) *Comprehensive Asymmetric Catalysis*; Vol. *1*−*3*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999. (b) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008.

(2) (a) Pfaltz, A.; Drury, W. J., III *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5723. (b) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691.

(3) (a) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932. (b) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.

(4) (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. (b) Berthod, M.; Mignani, G.; Woodward, G.; Lemaire, M. *Chem. Rev.* **2005**, *105*, 1801.

(5) (a) Alcock, N. W.; Brown, J. M.; Hulmes, D. I. *Tetrahedron: Asymmetry* **1993**, *4*, 743. (b) Fernández, E.; Guiry, P. J.; Connole, K. P. T.; Brown, J. M. *J. Org. Chem.* **2014**, *79*, 5391.

(6) (a) Brown, J. M.; Hulmes, D. I.; Guiry, P. J. *Tetrahedron* **1994**, *50*, 4493. (b) Doucet, H.; Fernandez, E.; Layzell, T. P.; Brown, J. M. *Chem. - Eur. J.* **1999**, *5*, 1320. (c) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763. (d) Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8702. (e) Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174. (f) Carroll, M. P.; Guiry, P. J.; Brown, J. M. *Org. Biomol. Chem.* **2013**, *11*, 4591.

(7) (a) McCarthy, M.; Guiry, P. J. *Tetrahedron* **1999**, *55*, 3061. (b) McCarthy, M.; Goddard, R.; Guiry, P. J. *Tetrahedron: Asymmetry* **1999**, *10*, 2797.

(8) Kwong, F. Y.; Yang, Q.; Mak, T. C. W.; Chan, A. S. C.; Chan, K. S. *J. Org. Chem.* **2002**, *67*, 2769.

(9) Knopfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971.

(10) Cardoso, F. S. P.; Abboud, K. A.; Aponick, A. *J. Am. Chem. Soc.* **2013**, *135*, 14548.

(11) For general references, see: (a) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771. (b) Harutyunyan, S. R.; den Hartog, T.; Geurts, K.; Minnaard, A. J.; Feringa, B. L. *Chem. Rev.* **2008**, *108*, 2824. (c) Alexakis, A.; Bäckvall, J. E.; Krause, N.; Pàmies, O.; Diéguez, M. *Chem. Rev.* **2008**, *108*, 2796. (d) *Catalytic Asymmetric Conjugate Reactions*; Cordova, A., Ed.; Wiley-VCH: Weinheim, Germany, 2010. For leading references on catalytic enantioselective alkynylation reactions, see: (e) Nishimura, T.; Guo, X.-X.; Uchiyama, N.; Katoh, T.; Hayashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 1576. (f) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963. (g) Yazaki, R.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 10275. (h) Li, C.-J. *Acc. Chem. Res.* **2010**, *43*, 581. (i) *Modern Alkyne Chemistry: Catalytic and Atom-Economic Transformations*; Trost, B. M.; Li, C.-J., Eds.; Wiley-VCH: Weinheim, Germany, 2015. (j) Fu, H.; Shen, P.-X.; He, J.; Zhang, F.; Li, S.; Wang, P.; Liu, T.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2017**, *56*, 1873.

(12) (a) Dumas, A. M.; Fillion, E. *Acc. Chem. Res.* **2010**, *43*, 440. Ivanov, A. S. *Chem. Soc. Rev.* **2008**, *37*, 789. (b) Fillion, E.; Fishlock, D.; Wilsily, A.; Goll, J. M. *J. Org. Chem.* **2005**, *70*, 1316. (c) Chen, B. C. *Heterocycles* **1991**, *32*, 529.

(13) (a) Knopfel, T. F.; Zarotti, P.; Ichikawa, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 9682. (b) Fujimori, S.; Knopfel, T. F.; Zarotti, P.; Ichikawa, T.; Carreira, E. M.; Boyall, D. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 1635. (c) Fujimori, S.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4964. (d) Zarotti, P.; Knopfel, T. F.; Aschwanden, P.; Carreira, E. M. *ACS Catal.* **2012**, *2*, 1232.

(14) Fillion, E.; Zorzitto, A. K. *J. Am. Chem. Soc.* **2009**, *131*, 14608.

(15) Carreira, E. M. U.S. 20050277772, 2005.

(16) Cui, A.; Walker, S. D.; Woo, J. C. S.; Borths, C. J.; Mukherjee, H.; Chen, M. J.; Faul, M. M. *J. Am. Chem. Soc.* **2010**, *132*, 436.

(17) For leading references, see: Trost, B. M.; Masters, J. T.; Taft, B. R.; Lumb, J. − P. *Chem. Sci.* **2016**, *7*, 6217 and references cited therein..

(18) Paioti, P. H. S.; Abboud, K. A.; Aponick, A. *J. Am. Chem. Soc.* **2016**, *138*, 2150.

(19) (a) Pappoppula, M.; Cardoso, F. S. P.; Garrett, B. O.; Aponick, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 15202. (b) Pappoppula, M.; Aponick, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 15827.

(20) Guiry, P. J.; Saunders, C. P. *Adv. Synth. Catal.* **2004**, *346*, 497.

(21) See Supporting Information for full details.

(22) For leading references, see: Sheldon, R. A. *Green Chem.* **2005**, *7*, 267.

(23) (a) Xiang, J. N.; Karpinski, J. M.; Christensen, S. B., IV. WO 0009116, 2000. (b) Houze, J.; Liu, J.; Ma, Z.; Medina, J. C.; Schmitt, M. J.; Sharma, R.; Sun, Y.; Wang, Y.; Zhu, L. U.S. 7,465,804, 2008. (c) Brown, S. P.; Dransfield, P.; Fu, Z.; Houze, J.; Jiao, X.; Kohn, T. J.; Pattaropong, V.; Vimolratana, M.; Schmitt, M. J. WO 2008130514, 2008. (d) Shimada, T.; Ueno, H.; Tsutsumi, K.; Aoyagi, K.; Manabe, T.; Sasaki, S.; Katoh, S. WO 2009054479, 2009. (e) Bharate, S. B.; Nemmani, K. V. S.; Vishwakarma, R. A. *Expert Opin. Ther. Pat.* **2009**, *19*, 237.

(24) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

(25) (a) Kondo, K.; Kan, K.; Tanada, Y.; Bando, M. *J. Med. Chem.* **2002**, *9*, 3805. (b) Nakamura, S.; Hirano, T.; Tsujimae, K.; Aoyama, M.; Kondo, K.; Yamamura, Y.; Mori, T.; Tominaga, M. *J. Pharmacol. Exp. Ther.* **2000**, *295*, 1005. (c) Nakamura, S.; Hirano, T.; Onogawa, T.; Itoh, S.; Hashimoto, A.; Yamamura, Y.; Kondo, K.; Mori, T.; Kambe, T. *J. Pharmacol. Sci.* **2004**, *94*, 426. (d) Nakamura, S.; Hirano, T.; Yamamura, Y.; Itoh, S.; Kondo, K.; Mori, T.; Kambe, T. *J. Pharmacol. Sci.* **2003**, *93*, 484.

(26) Omar-Amrani, R.; Thomas, A.; Brenner, E.; Schneider, R.; Fort, Y. *Org. Lett.* **2003**, *5*, 2311.

DOI: 10.1021/jacs.7b00363
J. Am. Chem. Soc. 2017, 139, 3352−3355